THE ANTIHISTAMINES

Their Clinical Application

SAMUEL M. FEINBERG, M.D.

Associate Professor of Medicine, Chief of Division of Allergy and Director of Allergy Research Laboratory

SAUL MALKIEL, Ph.D., M.D.

Assistant Professor of Medicine, Director of Research, Allergy Research Laboratory

ALAN R. FEINBERG, M.D.

Clinical Assistant in Medicine, Attending Physician in Allergy Clinic

Northwestern University Medical School

THE YEAR BOOK PUBLISHERS · INC.

200 EAST ILLINOIS STREET · CHICAGO

Preface

IT WAS BUT NATURAL that the establishment of the prominence of the role of histamine in the mechanism of anaphylaxis and allergy would lead to an intensive search for substances which would combat histamine. The most profitable find in this hunt has been the discovery of the "antihistamines"—substances which combat histamine by competing with the latter on the cell receptors. The pioneering work of Fourneau, Bovet, Staub, Halpern and others in Europe was soon followed by the production of compounds which could be used clinically. Our interest in the field began with our preliminary experience early in 1945 when we were able to procure Antergan from France and Benadryl in this country.

During the past few years there have been intensive activity and rapid progress in this field, particularly in this country. From hundreds of compounds screened in laboratories about a score has been skimmed off as the cream of the crop for marketing. It is not surprising that here and there some low grade cream has been

PRINTED IN THE U.S.A.

antihistamines might be considered. The clinical work is based in large part on our own experience with several thousand therapeutic case-trials It is also, of course, supplemented by the experience of others. In all reports, whether clinical or experimental, because of the nature of the book, it has been necessary to exclude the bulk of published papers. We are aware that we have omitted good ones as well as poor ones. Our only excuse is that we have been compelled to restrict ourselves to a limited number of references, however, we have endeavored to make these as representative as possible.

The book is divided into two sections, clinical and experimental Although the purpose of this manual is to present the clinical application of the antihistamines, we have felt that for an intelligent understanding of therapy experimental findings cannot be ignored. However, the separation of the volume into two sections should enable the physician to refer easily to either portion The experimental section is not exhaustive and the experimentalist engaged intensively in this field must perforce seek original sources. Nevertheless, this section can serve as an adequate starting point for the investigator to whom this field is relatively new.

We believe that the Appendix, which tabulates all known American products of antihistamines (except those sold directly to the public), will be of practical utility to the practitioner We have made reasonable efforts to make it complete and up to date.

A number of associates have participated in the development of the experimental and clinical facts presented by us. Among those to whom we owe a debt of

saved and a richer product left behind. The concentrated experimental interest was diffused into the broader phase of clinical trial and to a still wider sphere of general clinical therapy. A voluminous literature of several thousand articles on the clinical and experimental phases of the antihistamines has resulted. The interest in the antihistamines finally became truly widespread when lay attention was involved as a result of publicity, advertising and the permission for over-the-counter sale of some of these compounds. At first utilized in a limited way in allergic manifestations, the antihistamines came to be employed in a number of other syndromes, including the common cold. The multiplicity of compounds, the various forms of the antihistamines creating virtually hundreds of antihistaminic products, the thousands of published articles, the claims and counterclaims of superiority and individuality by virtually all the pharmaceutical manufacturers of these compounds and the even more laudatory claims of each pharmaceutical representative have combined to produce utter confusion in the mind of the practitioner.

Our purpose here is to condense the facts, crystallize the essence and present the practical application of our knowledge of the antihistamines. Since in our laboratory and clinic we have pursued a study of these drugs from the very beginning and have studied almost all of those now marketed, often being the first to examine them clinically, we feel that we have a justification and obligation to prepare such a review.

This volume is primarily clinical, intended for every physician in any field of medicine in which the use of

Table of Contents

Experimental Studies

1. Histamine 13
   Role in Anaphylaxis 14
   Pharmacology and Physiology 20
   Role in Allergy 23
   Combating Histamine 24
2. The Chemistry of the Antihistamines . . . 35
   Distribution and Metabolism 48
   Detection and Determination 50
3. The Pharmacology of the Antihistamines . . 52
4. Antihistamines in Experimental Hypersensitivities 73
   Anaphylaxis 73
   Influence on Other Immunologic Responses . 81
5. Bioassay in Man 86

Clinical Observations

6. Respiratory Allergy 103
   Hay Fever and Perennial Vasomotor Rhinitis . 103
   Asthma and Allergic Cough 112
   Individual Drugs—Results 114

appreciation are Dr. Sidney Friedlaender, Dr. Theodore *B. Bernstein and Miss Betty J Hargis.* We are also grateful to members of the Department of Pharmacology, Dr. Carl A Dragstedt, Dr. J. A Wells and Dr. Karl F. Urbach for their numerous aids in our experimental program We are especially appreciative of the help and friendship of Dr Bernard Halpern of Paris, whose unstinting help and exchange of experiences have been an inspiration. We wish to take this occasion also to thank our many friends in the pharmaceutical industries who gave helpful advice or material assistance to enable us to carry on the experimental and clinical work. And finally, we are not unmindful of the warm, cooperative spirit and patience of the publisher's staff

—S M F
—S M
—A. R. F

7. Dermatoses 131
Urticaria and Angioneurotic Edema . 131
Serum Sickness Syndrome . . 136
Dermographism . 138
Atopic Dermatitis (Eczema) 139
Contact Dermatitis 142
Pruritus 143
8 Miscellaneous Manifestations 146
Allergy to Injected Agents 146
Diseases of the Eye 147
Collagen Diseases 149
Tuberculosis 150
The Common Cold . 151
Gastrointestinal Disease 158
Motion Sickness, Nausea and Vomiting 159
Radiation Sickness 161
Diseases of the Nervous System 162
Other Conditions 165
9. Administration and Dosage 168
Conditions Determining Size of Dose 168
Dosage of Individual Drugs 171
Frequency of Administration 176
Selection of Antihistamine 178
Drug Combinations 180
Method of Administration 183
10. Toxic Effects 191
Common and Minor Side Actions . 192
Toxicity Features of Individual Drugs 196
Severe or Unusual Effects and Special Studies 203
Self-Medication—Its Hazards . 213
Appendix Proprietary Antihistaminic Preparations 220
References . . . 232
Index . 277

CHAPTER 1

Histamine

In a consideration of the therapeutic effects of the antihistamines it is proper to consider the evidence on which is based the conclusion that histamine does play a part in anaphylaxis and allergy. The fact that the significance of histamine has been discussed many times indicates that the question has not been settled beyond dispute; however, there are but few antagonists to the fundamental concept that histamine is related causally to the phenomena of anaphylaxis and that it is likewise related causally, albeit by analogy, to the phenomena of allergy.

The subjects of anaphylaxis and histamine are inextricably interwoven in the literature, and it will be seen that not only do anaphylactic shock and histamine shock strikingly resemble each other but the agents which prevent one will prevent the other. The term anaphylaxis was apparently originated by Portier and Richet (428) in 1902 to describe the phenomenon of sudden death which occurred in dogs which had been reinoculated with the toxins extracted from the sea anemone The

ment of histamine came from Dale (117) in 1929. He stated that "we may picture the anaphylactic shock, therefore, as the result of cellular injury, due to the intracellular reaction of the antigen with an aggravating antibody. Whether this is general or localized in a particular organ, histamine will be released and its effects will be prominent in the resulting reaction imposing a general resemblance to the syndrome produced by histamine itself, on the symptoms seen in each species The cell injury, however, is not limited to the degree required to produce a release of histamine, and involves other and more direct results Such a conception is in accordance with all the facts as yet available, and it has the advantage of rendering intelligible, not only the striking resemblance between symptoms of the anaphylactic reaction and those produced by injecting histamine, but also the various and equally significant points of difference between the two syndromes."

The first important experiments designed to demonstrate an actual release of histamine in association with the anaphylactic reaction were those of Watanabe (558). He indicated that there probably were differences in the histamine content of the dog's liver and the guinea pig's lung before and after shock. The word "probably" is Dragstedt's (134) who indicated that Watanabe did not examine the tissues of the same animal before and after shock because he knew there was a pronounced variation from animal to animal in the tissue content of histamine However, Dragstedt and Gebauer-Fuelnegg (136, 220) and Bartosch, Feldberg and Nagel (28) soon verified the histamine hypothesis

relationship between anaphylaxis and allergy may be difficult to reconcile since we have come to regard allergy as any manifestation of specific hypersensitiveness, exclusive of the anaphylaxis produced in experimental animals. Nevertheless, these phenomena are related and there is abundant evidence that histamine plays the major villainous role in both sequences (91, 134, 449).

Role in Anaphylaxis

The identification of histamine as a constituent in various animal tissues by Barger and Dale (27), Abel and Kubota (4) and others enhanced the plausibility of its involvement in anaphylactic reaction because by about the same time Friedemann's (200) concept of a humoral mechanism for shock had lost a good deal of its force. Dale and Laidlaw (118) in 1911 had already demonstrated that histamine injections caused symptoms which were similar to anaphylaxis The identification of histamine in normal tissues came in 1927 when Best *et al* (36) demonstrated its presence, especially in the lungs, in quantities adequate to serve, physiologically, as a possible source of histamine within the organism in the event that it might be released. These observations together with those of Lewis and Grant (343) and Hare (263), who isolated from urticarial wheals an H-substance which would stimulate uterine contractions, and of Lewis (342), who expressed a concept of anaphylaxis involving an H-substance liberated from the cells, revived the dormant interest in the possibility that histamine was the long-sought common denominator in anaphylaxis and allergy. The all but complete indict-

Zinsser who stated that allergy in man "is based on an immunological mechanism basically identical with anaphylaxis in animals, specifically modified by human anatomical and physiological conditions." (2) There is abundant evidence that histamine occurs in human tissue as well as in animal tissues and that it occurs in adequate amounts to produce pharmacologic symptoms. (3) There is sufficient evidence that the effects of histamine are qualitatively consistent with certain allergic manifestations. (4) Histamine, or at least a histamine-like substance, is actually released during allergic reactions in man, and (5) the therapeutic measures which counteract the effects of histamine are of value in the treatment of allergic manifestations

The protagonists of the histamine theory are not without their opponents, however. One of the earliest challenges arose from the observations of Friedberger *et al.* (199) that desensitized or antianaphylactic guinea pigs do not show desensitization to histamine, nor does histamine desensitize the animals to the antigen. Wells (566) pointed out that histamine should not be expected to desensitize if it is the product of the antigen-antibody reaction, since it is this reaction alone that is prevented by desensitization. Wells (565), however, did sum up certain objections to the histamine theory as follows: (1) Histamine fails to desensitize animals or tissues although it produces strong reactions in uterine muscle strip which has been desensitized. (2) Histamine does not produce the temperature reactions or the coagulation changes commonly seen in anaphylaxis. (3) Quinine augments the susceptibility of sensitized ani-

and showed that histamine was liberated during an anaphylactic reaction in an intact animal. Dragstedt and Mead (137) showed that the striking increase in the histamine of the blood and lymph of dogs after anaphylaxis was sufficient to explain the shock, and Code (89) noted that the amounts of histamine liberated in shocked guinea pigs were sufficient to produce anaphylactic symptoms.

These and succeeding events seem to constitute a valid argument that histamine is undoubtedly a potent factor in the production of the symptoms of anaphylactic shock. However, evidence for its role in the mechanism of production of allergic manifestations in man, one of us (174) stated, "has not kept pace with that for anaphylaxis in animals." This situation is readily understood, for controlled studies on allergic shock in man are not feasible and, further, the amount of histamine in allergic manifestations in man is quantitatively much less than it is in anaphylaxis in animals. With respect to the histamine concept of anaphylaxis and allergy, Dragstedt (133) outlined the possible theoretical approaches to the control of allergic reactions. They are (1) reduction of histamine available for liberation, (2) prevention of liberation of histamine, (3) inactivation of released histamine and (4) decrease of effects of histamine. Several points of circumstantial evidence which Dragstedt (135) proposed indicate that histamine plays an important role in human allergy. (1) There is the analogy which exists between anaphylaxis in animals and allergic reactions in man. There are both similarities and differences in these reactions, but he agreed with

of anaphylaxis, such as diminished blood coagulation (286) and the anticomplementary effects. Segal *et al.* (488) appear in doubt as to whether the toxic substance

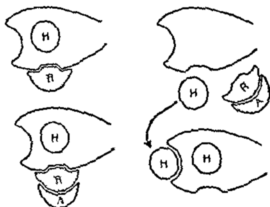


FIG. 1.—Histamine release mechanism in allergy (some of these diagrammatic concepts are theoretical). *Top left*, sensitized cell. Allergic cell has attached sensitizing antibodies, the reagins *R*. All cells, allergic or not, have histamine or its precursor, *H*, which causes no harm while within the cell. *Bottom left*, antigen reagin union. Antigen *A* unites with reagin *R* on the sensitized cell. *Right*, release and action of histamine. Union of antigen and reagin causes release of histamine from within sensitized cell. (Histamine from such cells or unsensitized cells may also be released by other stimuli.) This histamine is free to attach to receptors on adjacent cells, causing damage which results in allergic symptoms.

released by the cells of the shock organ is histamine-like or choline-like; Farber and co-workers (165) found no evidence to indicate that acetylcholine was released in greater amounts from lungs and intestines of sensi-

mals to foreign protein yet it does not affect the intoxication caused by histamine. Again, contrary evidence to the histamine theory may, perhaps, be accepted from the work of Code and Hester (92), who observed a fall in the blood histamine of the calf and the horse during anaphylaxis, and of Rose and Weil (460, 461), who made similar observations in the rabbit. The latter, apparently contradictory, findings but serve to strengthen the histamine hypothesis, according to Dragstedt (134), for he and his co-workers (138) demonstrated that the addition of antigen to the blood as it is perfused through the lungs of a sensitized rabbit results in both a leukopenia and a decreased histamine content in the recovered blood. This result can be fully appreciated when it is disclosed that Code (90) had previously shown that the leukocytes of rabbit's blood contain a large amount and a substantial portion of the whole blood histamine and that Katz (299) found that the addition of antigen to the blood of the sensitized rabbit resulted in release of histamine from the blood cells. The failure to detect an elevated blood level of histamine does not negate the evidence that histamine is involved in tissue reactions, for histamine leaves the blood stream with extreme rapidity and extraction methods do not always detect physiologically active amounts.

Actually, the histamine theory of anaphylactic shock is tenable only as a partial explanation. Even Dale's (117) statement of the hypothesis is explicit in this respect. The theory can explain smooth muscle contraction, capillary dilatation and permeability and glandular secretion. Heparin activity accounts for other features

Physiologic studies of histamine reveal that it is a powerful vasodilator in certain species. If injected locally into the skin, capillaries in contact with the drug dilate and there results a reddening known as a flare, followed shortly by a localized edema known as a wheal. The wheal is caused by the passage of considerable plasma protein and fluid into the extracellular space of surrounding tissues by virtue of the change of permeability of vessel walls In the cat and rat a constriction re-

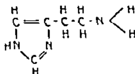


Fig. 2—Histamine

sults, in contrast to the dilatory effects in man, monkey and dog Histamine acts on the heart indirectly, principally through reflex action from vasodilatation. Smooth muscle is stimulated by direct action and many studies on uterine muscles and the musculature of the bronchioles have been made. Histamine is believed to be identical with the secretagogue gastrin, because it is a powerful stimulant of the gastric glands as well as of other glands. Histamine or a histamine-like substance is released from tissue cells by stimuli such as toxins, venoms and acute burns as well as in anaphylaxis in animals and in allergic conditions in man. It is apparently excreted by the kidney and inactivated in the kidney, lung and liver by an enzyme, histaminase. Both the adrenal me-

tized guinea pigs shocked in vitro than from normal lungs or intestines.

Pharmacology and Physiology

It may seem remiss to discuss the chemistry and physiology of histamine after the presentation of its role in anaphylaxis, but since the physiology and pharmacology is to be presented in somewhat greater detail in a later chapter there seems to be some justification. Chemically, histamine is β-iminazolyethylamine, the structural formula appears in Figure 2. It was synthesized by Windaus and Vogt (575) in 1907. Actually, histamine is a decarboxylation product of the amino acid, histidine, which is present in all complete proteins, and the early studies of Ackermann and Kutscher (7) indicated that various bacteria could accomplish this decarboxylation.

Histamine is a strongly basic, water soluble, white crystalline organic compound which is usually dispensed as the phosphate salt. The detection and determination of histamine has been essentially by bioassay technics, involving methods such as contraction of guinea pig ileum or uterine horn. Advances in paper chromatography have resulted in technics for the identification of histamine in blood (548), urine and feces (547). Quantitative measurements have been made by such bioassay technics as comparisons with the fall of blood pressure produced by a standard histamine dose. Colorimetric chemical methods have also been described (26). The isolation of histamine in a high state of purity and in quantitative amounts from biologic fluids has recently been accomplished (370).

matory cell exudate about blood vessels. Atelectatic areas were also found in the lungs (172).

Role in Allergy

The relationship of histamine to allergy up to this point has been considered essentially by inference, but evidence has accumulated over recent years which indicates its presence or release in allergic manifestations. The absence or presence of histamine, however, is relatively of no significance in assigning the odium, allergic manifestation, to any given condition. Thus, Katz and Cohen (301) found an in vitro release of histamine when the blood of an allergic person was incubated with the specific allergen. Similarly, histamine was released into blister fluid when the allergen was injected locally into clinically sensitive patients (300). Although Rose (453) reported pronounced fluctuation of the histamine content in the blood of patients suffering from diverse allergies, urticaria excepted, Giunchi and Serafini (227) found normal values in most subjects with hay fever a certain number of the patients showed high values. Hjort, Worden and Hagle (270) also failed to find any spectacular increments of histamine in either active or latent allergic states. Specific desensitization did not produce an increase in the histamine content (227) although physical exercise did (493, 494). Control nonallergic subjects were normal under all circumstances Rose (455) determined that asthmatic patients excreted large amounts of histamine in the urine, compared with those for normal persons. In addition, he and his co-workers (456) found that certain tissues of

dulla and cortex are involved in the regulating mechanism of histamine metabolism. In addition to the metabolism, Urbach (547) suggested that histamine is acetylated in the intestinal contents to acetyl histamine which is partially absorbed from the intestinal tract and excreted in urine (12, 464) as well as in feces.

Some histamine effects other than those which will be discussed from a pharmacologic viewpoint or which result in specific allergic manifestations are interesting enough to warrant brief mention. Rose (452) found that enough histamine could be injected so that definite symptoms of histamine intoxication appeared but without a demonstrable increase in the blood histamine levels which were determined periodically. This seems to indicate that the effect is apart from the action of blood histamine which disappears rapidly and probably acts cellularly. The basal metabolic rate rises during the intravenous administration of histamine. This increase is transitory and drops soon after the drug is stopped (425). Histamine given to asthmatic patients by any route caused a definite but variable bronchoconstriction, measured by the reduction in vital capacity No significant reductions were noted in normal control subjects or in patients having histories of other severe allergic tendencies (111). The repeated administration of histamine to experimental animals produced an inflammatory reaction in the vascular system of the lung and heart in the endo- and myocardium. Certain lesions common in all species of animals were edema of the endocardium, inflammatory cell collections in the myocardium, edema of the heart valves and perivascular edema and inflam-

matory cell exudate about blood vessels. Atelectatic areas were also found in the lungs (172).

Role in Allergy

The relationship of histamine to allergy up to this point has been considered essentially by inference, but evidence has accumulated over recent years which indicates its presence or release in allergic manifestations. The absence or presence of histamine, however, is relatively of no significance in assigning the odium, allergic manifestation, to any given condition. Thus, Katz and Cohen (301) found an in vitro release of histamine when the blood of an allergic person was incubated with the specific allergen. Similarly, histamine was released into blister fluid when the allergen was injected locally into clinically sensitive patients (300). Although Rose (453) reported pronounced fluctuation of the histamine content in the blood of patients suffering from diverse allergies, urticaria excepted, Giunchi and Serafini (227) found normal values in most subjects with hay fever a certain number of the patients showed high values. Hjort, Worden and Hagle (270) also failed to find any spectacular increments of histamine in either active or latent allergic states. Specific desensitization did not produce an increase in the histamine content (227) although physical exercise did (493, 494). Control nonallergic subjects were normal under all circumstances Rose (455) determined that asthmatic patients excreted large amounts of histamine in the urine, compared with those for normal persons. In addition, he and his co-workers (456) found that certain tissues of

allergic man, such as antral mucosa, skin and lung, were much richer in histamine than similar tissues from nonallergic subjects. For example, lung tissue from asthmatics contained as much as 115 μg. per Gm. compared with 15–35 μg. per Gm. for normal lung tissue. Urticarial skin lesions were found definitely to have a lower histamine value than normal or surrounding healthy skin (406, 413, 419). From studies on the effect of various antihistamines on experimental sensitizations, Mayer (385) was forced to conclude that an H-substance plays an important role in contact dermatitis. Because of current interest, it is noteworthy to report that no striking difference was found in total histamine activity between secretions of the "common cold" and those of allergic rhinitis, although concurrent control examinations of "normal" secretions were not done (541). There was no correlation between the number of eosinophils and the amount of histamine.

Combating Histamine

The evidence assigning histamine an active role in allergy and anaphylaxis prompted observers to attempt methods of reducing histamine manifestations. These methods, if they are to be effective, must be based on one or more of the following sequences of events: (1) preventing the antibody-antigen union, (2) modifying the action of the liberated histamine by drugs which have a reversing action (epinephrine); (3) inactivating the histamine (histaminase); (4) desensitizing the tissues against the action of histamine by graded doses of histamine itself; (5) blocking the action of the hista-

mine by compounds which unite with or compete for histamine or which fix themselves on the effector cells and so inhibit action of histamine; (6) preventing the formation or release of histamine (antihistaminogenesis).

Initial attempts were based on the belief that tolerance for histamine in man and in animals might be

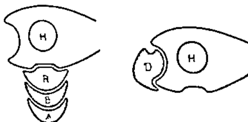


FIG. 3—Methods of combating histamine *Left*, desensitization Desensitization produces blocking antibody *B*, which attaches to reagin *R* and prevents union of reagin and antigen *A* *Right*, chemical block. Antihistaminic drug *D* attaches to histamine receptor, thus blocking attachment of released histamine

raised through appropriate procedures. Closely related was the attempt to desensitize the individual on the basis that he was sensitive to histamine. Much study was given to this method of attacking the problem and widely varying reports of success and failure in various allergic conditions appeared in the literature. The more recent experiments of Farmer (166) suggested that desensitization to histamine, determined by the uterine strip method, might be possible in guinea pigs This could be accomplished both by parenteral and by oral administration (167). In this, he apparently corroborated earlier

work, such as that of St. Karady (476), and was in turn substantiated by Karady (297) and Essex and Horton (160) in 1941. Some evidence (188), too, has accumulated from our laboratory that guinea pigs can be made more resistant to histamine. Tolerance has been reported (163, 302) in other animals, although Wells, Gray and Dragstedt (567) stated that they failed to modify the histamine tolerance in dogs, and Farmer (168, 169) noted that histamine pretreatment had no effect on the establishment of active sensitization on the uterine strip contraction to the antigen in egg-white–sensitized guinea pigs.

Wells and his associates (567) criticized much of the previous work because of the inconsistent results and because the procedures, in many instances, bore little resemblance to the desensitization which is used clinically. This latter comment is especially valid. In this respect, too, it is noteworthy that Selye (491) has indicated that single or repeated injections of toxic doses of many drugs produce the "alarm reaction" which is followed by a nonspecific tolerance. This concept is particularly interesting because Selye (490), in comparing symptoms of the first stage of the alarm reaction with those of histamine poisoning and anaphylactic shock, found that the liberation of large quantities of histamine or similar substances from tissues is probably the common factor for the similarity in the symptomatology. The second stage is associated with an enlargement of the adrenal cortex and an increased elaboration of the adrenotrophic principle from the pituitary.

Nevertheless, despite the theoretical objections, clin-

ical treatment in certain cases seems to offer some evidence favoring the validity of the sensitivity theory. Horton (275) reported that he reduced the frequency and severity of headaches due to histaminic action by the injection of small doses of histamine. Additional reports on histamine desensitization therapy have appeared in which promising results were obtained in such conditions as perennial and seasonal allergic rhinitis (170, 171, 313), eczema and contact dermatitis (313), penicillin drug sickness (431) and migraine (373, 537). In evaluating this use of histamine, Curry (113) stated that desensitization is recommended in the treatment of histamine cephalalgia, migraine and Ménière's disease. One of us (174) had previously taken the stand which summarized the then current opinion of most clinicians that the effectiveness of histamine in allergic conditions was exaggerated and that whatever beneficial results were obtained must be explained on a basis other than desensitization. Recent reports make one now hesitate to speak with that degree of finality and skepticism and should be further evaluated and corroborated *even though* the criticisms (567) and the findings of Selye (490–492) would still be tenable.

Desensitization to histamine received a different approach with the work of Fell, Rodney and Marshall (191, 451). They were of the opinion that, since histamine failed to produce antibodies in allergic patients, application of the theory of hapten action, so ably demonstrated by Landsteiner (322), to a histamine-protein conjugate might prove effective In their work on animals they found that, although specific antiserums of

high precipitin titer could not be produced, specific cross reactions to the hapten occurred and histamine would inhibit the specific reaction. Animals immunized to the histamine azoprotein (Hapamine) were definitely more resistant to anaphylaxis and the effects of histamine. Apart from their clinical results (96, 497), the experimental findings were criticized by Coffin and Kabat (93) who failed to confirm the results on the protection of immunized animals against histamine and to establish whether any antibodies were formed to the haptenic histamine. Farmer (169) also failed to modify the uterine strip reaction in egg-white–sensitive guinea pigs pretreated with histamine azoprotein. Finally, reports (143, 266) have appeared which fail to substantiate clinical use of this substance, these experiences seem to be in accord with those of most clinicians (174).

In 1929, Best (35) showed that some tissues contain an enzyme capable of destroying histamine and it was subsequently demonstrated that such destruction occurred when the two were mixed and incubated. It naturally followed that here might be a means of combating histamine manifestations in their relation to allergy. Corroborating the clinical observation that women often enjoyed a remission from allergic manifestations during pregnancy were the findings that the blood of pregnant women had a high histaminolytic activity which was correlated to its increased histaminase content (13, 287, 296, 532). Rose *et al.* (457), confirming the observation of an elevated plasma histaminase level in pregnant women, also showed that a deficient histaminase level was present when asthma persisted during preg-

nancy (458). However, animal experiments (331, 467) have failed to reveal usefulness of histaminase as a histamine combatant, despite the results of Karady and Browne (298), which could not be confirmed (37, 113).

As histamine or a histamine-like substance began to be more and more accepted as an important factor in allergy and anaphylaxis, increased attention was given to the development of histamine-inhibiting agents, specific and nonspecific. An excellent review by Hill and Martin (268) appeared as early as 1932 listing 165 substances or methods which had been described in experiments to inhibit anaphylactic shock. Among the agents which showed evidence of some inhibiting action were atropine, barium chloride, barium sulfate, reduction of barometric pressure, chloral hydrate, heparin, benzol in large dose before and during sensitization, intercurrent infection with tuberculosis, sodium bicarbonate and multiple sensitization and treatment with one of the several antigens. In subsequent years many more nonspecific means were utilized in an attempt to inhibit anaphylactic and histamine shock; since none of these proved of decided clinical value, only those observations will be considered which seem to be of theoretical interest.

Rattlesnake venom (crotalin) has occasionally been used. The experiments of Frank (197) indicated that although crotalin protects against anaphylactic shock the mechanism is that of a histamine release which produces an increased tolerance for the histamine. The rationale of potassium therapy in allergy may have some basis,

for Carlson and Whitehead (77) observed that potassium salts are of value in prevention of deaths (60–75 per cent) against the minimum lethal dose of the antigen in sensitized animals. However, no clinical results were observed with this therapy in allergic manifestations (472a). The widespread use of salicylates in the treatment of rheumatic fever prompted many investigators to note their effects on immunologic processes. Campbell (73) reported that acetylsalicylic acid temporarily interfered with the antibody-antigen reaction in anaphylaxis but although it was a true antianaphylactic drug it did not counteract histamine. These findings were disputed by Swyer (534), who noted that salicylate had an antihistaminic effect on the spreading of histamine, whereas Smith and Humphrey (507) claimed that sodium salicylate in blood concentrations as high as 50 mg per 100 ml. conferred no appreciable protection against acute anaphylactic shock. On the other hand, salicylate exerted a protective action on passive Arthus' reactions and especially on Shwartzman phenomena, indicating that the effect was not a direct antihistaminic effect but appeared to be due to some action on the local blood capillaries.

Current interest seems high with respect to the adrenocorticotrophic hormone (ACTH) and cortisone, especially since the reports (43, 44, 150, 233, 433, 454, 459) on their use in allergic manifestations. Animal experiments were thereupon conducted to determine the effect of ACTH and cortisone in anaphylactic and histamine shock. Although Orskov (411) claimed to have protected sensitized guinea pigs against passive anaphy-

laxis by ACTH, the report of Leger, Leith and Rose (328) and our preliminary work (377) indicate that pretreatment of animals with ACTH or cortisone fails to protect guinea pigs against active sensitization and shock, passive anaphylactic and histamine shock.

One of the first groups of agents found to have the property of inhibiting the characteristic actions of histamine in laboratory animals was demonstrated by Edlbacher, Jucker and Baur (147) to be certain of the amino acids. These amino acids, cysteine, histidine and derivatives and arginine and derivatives were also used by many other investigators (144, 318, 450, 503). Some basis for their use may be the following: Ackermann (6) assumed that the imine group in arginine and histidine would compete for the identical group of the imidazol ring of histamine, the group believed to be responsible for its anchoring ability to the cell receptors. This was verified for the derivatives of Rocha e Silva (449, 450), and imidazol in the hands of Morris and Dragstedt (399) displayed an antihistaminic effect on isolated guinea pig intestine. These substances, however, were of too little effectiveness for therapy and of too high toxicity for use in either animals or man. Notwithstanding, clinical reports (292) on amino acid therapy of allergic diseases have appeared, but the results appear to be of questionable value.

The dawn of the antihistaminic era broke in 1933 when Fourneau and Bovet (195) reported that certain phenolic ethers had the property of inhibiting or counteracting the action of histamine and that the most effective of these was 2-isopropyl-5-methylphenoxyethyldi-

ethylamine, known as 929F. Staub and Bovet (517) found that although 929F had definite antianaphylactic properties, since it protected guinea pigs against two lethal doses of histamine, it also produced definite toxic effects in animals. Because of this toxicity, Staub (514) investigated a Fourneau compound which contained the ethylenediamine radical. This product, 1571F, described as N,N-diethyl-N′-phenyl-N′-ethyl-ethylenediamine, was also found to be antihistaminic and antianaphylactic. These initial investigations released the flood waters and in relatively rapid succession there appeared 2325RP, 2339RP (Antergan), 2786RP (Neo-Antergan), diphenhydramine hydrochloride, tripelennamine hydrochloride and many others with which we all are familiar. A more complete discussion of the chemistry of these compounds appears in the following chapter, and the pharmacologic and antianaphylactic effects are discussed in Chapters 3 and 4, respectively.

An intriguing approach to the prevention of histamine activity is through inhibiting histamine formation, that is, antihistaminogenesis. It was previously stated that histamine could be released from histidine by enzyme action and it is presumed that histidine decarbox*ylase is the enzyme which is partially responsible, at least,* for histamine formation in the animal body. Moreover, certain substances with phenolic hydroxyl groups were found to inhibit the action of histidine decarboxylase (30, 381, 572) in vitro. These substances, the flavonoids (vitamin P-like), were investigated some years ago and results of their use in the prevention of anaphylactic shock have since been the subject of controversy. The

early literature includes the reports of Hullstrung and Hach (278) who found pretreatment with vitamin P of no effect on anaphylaxis in the guinea pig, whereas Hiramatsu (269) found it effective. This subject was recently again brought into discussion by the discovery of the effect of rutin on capillary permeability. Thus Raiman, Later and Necheles (432) and Martin and Moss (382) stated that pretreatment with rutin is effective in protecting sensitized animals against anaphylactic shock, while at the same time an array of negative evidence was presented by Roth and Sheppard (471), Levitan (337, 338) and Arbesman, Neter and Becker (19). In support of the opposing forces is the inclusive report of Clark and Mackay (87) who studied over 15 flavonoid compounds, including rutin and citrin (vitamin P) Our own preliminary results (376) also showed that the catechins are without effect.

A few words will suffice to discuss therapy which is not designed to attack any of the events previously mentioned as occurring in the histamine sequence. Such methods of therapy, although essentially symptomatic, are here mentioned because they more or less deal with the repair of damage which results from the antibody-antigen mechanism or the histamine release The methods correcting histamine effects such as bronchoconstriction or secretion have been in popular use for some time. Epinephrine is usually the drug of choice in most cases of asthma and allergy. Its action on the bronchi is probably twofold. it constricts blood vessels, thus diminishing turgescence and swelling of the bronchial mucosa, and it stimulates the sympathetic nerve endings, thereby

antagonizing the bronchoconstrictive effect of the overstimulated vagus. Ephedrine, which has similar actions, is particularly useful as a substitute in mild attacks and when more prolonged action is needed. Its chief advantages over epinephrine are its effectiveness by oral administration and the longer duration of action. Its disadvantages are that its action is less complete and that often it has no effect at the height of the attack.

Drugs which may have a synergistic action when combined with ephedrine are theophylline, theobromine, sodium salicylate, theobromine calcium salicylate and similar drugs. Aminophylline (theophylline-ethylenediamine) given intravenously is a valuable drug although by no means effective in all asthmatic episodes. Some acute attacks are not relieved by this drug, and its behavior indicates that it is more effective in the severe and prolonged asthmatic attack than in the early acute attack. Aminophylline has a direct relaxing effect on bronchial musculature which has been constricted by histamine or anaphylactic reaction.

Iodides are among the oldest, time-honored remedies. Although their action is not entirely understood, it is evident that one effect is the production of a thin bronchial secretion The iodides are best suited to modify the pathologic phase of asthma wherein lies the production of a tenacious and highly viscous mucus which plugs the bronchioles and adds to the total bronchiolar obstruction. Other therapies include rectal ether in status asthmaticus, sedatives such as chloral hydrate, barbiturates, etc., aspirin, codeine, coffee, liquor, etc., all of which if used judiciously may at times produce the desired effect.

CHAPTER 2

The Chemistry of the Antihistamines

HAVING CONSIDERED the role that histamine plays in the anaphylactic and allergic reaction, it seems pertinent at this time to identify chemically, in a more detailed discussion, those compounds which we now know as the antihistamines Actually, the term "antihistaminic compound" has been under criticism (528). Antihistamines are but a special category of the spasmolytics, but justification for their classification is found in the extraordinary high specificity of these compounds in antagonizing the physiologic effects of histamine Further justification may be the close quantitative relationship between any given amount of histamine and the quantity of antihistamine necessary to antagonize it The high specificity immediately excludes some of the compounds antagonistic to histamine which were discussed in the preceding chapter, namely, the amino acids, histamine complexes, histamine azoprotein, atropine, epinephrine, aminophylline, etc

In 1933, Bovet and Maderni (50) and Fourneau and Bovet (195, 196) studied the sympatholytic activities of a series of compounds, including 929F, in connection with research for new antimalarials. The anti-anaphylactic capacity of 929F was described by Staub and Bovet (517) In 1939, another compound, 1571F, was found to be superior to others studied. Staub (514–516) discussed the two series which were represented by 929F (an ether) and 1571F (an amine). She found that the amines were more specifically antihistaminic in counteracting histamine shock, while the ethers, being less specific, were more effective in relieving histamine-induced bronchial asthma. This observation has since found some confirmation, probably because the *latter group contains those compounds which are more* sedative and antispasmodic

This discussion of the chemistry of the antihistamines will include those substances which have some interest historically, clinically or experimentally. For a more complete list and description of those which had been experimentally tried up to July 1947, the reader is referred to the excellent review of Huttrer (283). In this survey the amine type, represented by 1571F and its related ethylenediamine derivatives, will be presented in approximate chronological order, followed by discussion of the ether type, the monamines and a miscellaneous group.

Ethylenediamine Derivatives

1571F.—Compounds similar to 1571F, N,N-diethyl-N′-phenyl-N′-ethyl-ethylenediamine, were reported by

Braun and his co-workers (54) in 1917. Bovet and Staub (51) and Staub (514–516) investigated the antihistaminic and antianaphylactic properties and found that 1571F protected guinea pigs against 10 lethal doses

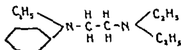


FIG. 4.—1571F.

of histamine. While rather nontoxic for animals, it was found to be extremely toxic to man.

2339*RP* (*Antergan*).—This compound, N,N-dimethyl-N'-benzyl-N'-phenyl-ethylenediamine, was described by Halpern (247) in 1942 as having been pre-

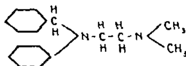


FIG. 5.—2339RP (Antergan).

pared in the Rhone-Poulenc laboratories He studied its pharmacologic and antihistaminic properties and compared its actions with those of 1571F and 2325RP, among others

Neo-Antergan.—The choice of nomenclature is perhaps bad for this drug, for it is not a derivative of Antergan. Rather, it is N,N-dimethyl-N'-p-methoxybenzyl-N'-2-pyridyl-ethylenediamine. Bovet and his associates

thiazine, was also synthesized by Gilman and Shirley (226). Pharmacologic and clinical studies were con-

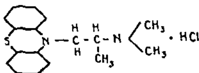


FIG. 8—3277RP (Phenergan).

trasted with those of 3015RP by Halpern and co-workers (253, 257) and 3277RP was found to be a much more effective antihistamine.

Pyribenzamine—The chemical description of N,N-dimethyl-N'-benzyl-N'-2-pyridyl-ethylenediamine was given by Huttrer *et al.* (284) in 1946. Mayer and co-workers (383, 390) found that, experimentally, Pyribenzamine (tripelennamine) had more striking antihis-

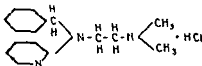


FIG. 9—Pyribenzamine

taminic properties than any of the previous preparations. Arbesman *et al* (18) found it to have a definite effect on histamine and allergic whealing and on that due to passive transfer when taken orally by human subjects. In 1946 Feinberg (174) also reported on its clinical efficiency to the Council on Pharmacy and Chemistry of the American Medical Association.



(176) noted an incidence of 70 per cent effectiveness during the 1947 ragweed and mold season.

Diatrin—This drug, N,N-dimethyl-N′-phenyl-N′-(2-thienylmethyl)-ethylenediamine, is the phenyl analogue of Histadyl. Leonard and Solmssen (332) synthesized this compound and Kyrides *et al.* (314) indicated that

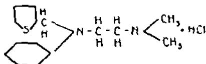


FIG. 12—Diatrin.

it was an effective antihistamine and antianaphylactic compound, its effectiveness being somewhat less than that of Pyribenzamine and only about two-thirds that of Antergan Our own limited clinical results show it to be moderately effective

Neohetramine—This drug was synthesized in the laboratories of the Nepera Chemical Company, and

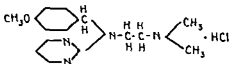


FIG 13—Neohetramine

Reinhard and Scudi (437) reported on the antihistaminic, antianaphylactic and toxic properties. This compound is N,N-dimethyl-N′-2-pyrimidyl-N′-p-methoxybenzyl-ethylenediamine. Bernstein and Feinberg (32)

Histadyl (Thenylene).—Weston (573) published an account of N,N-dimethyl-N′-2-pyridyl-N′-2-thenyl-ethylenediamine at about the same time it was reported independently by Clapp *et al.* (86) and Ercoli *et al.* (159) in other laboratories. Its effectiveness as an antihista-

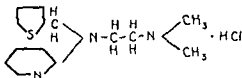


FIG 10—Histadyl (Thenylene)

mine, established by animal experiments, was indicated by Roth *et al.* (469), Ercoli *et al.* (159), Litchfield *et al.* (345) and Lee *et al.* (327). Lee, Dinwiddie and Chen (327) used this drug in hay fever patients and noted that in "a majority" symptoms were alleviated.

Chlorothen (Tagathen).—This chlorine analogue, N,N-dimethyl-N′-2-pyridyl-N′-5-chloro-2-thenyl-ethylenediamine, was also reported by Clapp *et al.* (86).

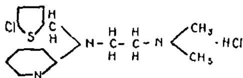


FIG 11—Chlorothen (Tagathen)

Litchfield and co-workers (345) investigated the pharmacologic properties and claimed that, compared with Pyribenzamine, chlorothen showed increased antihistamine activity and decreased toxicity. Clinically, we

(187) and, clinically, we (33) found it moderately effective but useful because of the low incidence and degree of sedation.

p-Fluorobenzyl-DPE (*Lederle*).—This compound, the fluorine derivative of Pyribenzamine, was synthesized by Vaughan and co-workers (554) and is known chemically as N,N-dimethyl-N′-p-fluorobenzyl-N′-2-pyridyl-ethylenediamine Litchfield *et al.* (346), as well as

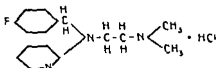


FIG. 16.—p-Fluorobenzyl-DPE (Lederle)

Vaughan (554), reported on its antihistaminic properties and found it to be more effective than Pyribenzamine For clinical results we again have to turn to our own (178) limited experience. The drug has been found as effective in 30 mg doses as most antihistamines in 50 mg doses

Thenfadil.—The synthesis of this compound, N,N-dimethyl-N′-2-pyridyl-N′-3-thenyl-ethylenediamine, was

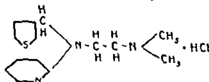


FIG. 17.—Thenfadil.

reported by Campaigne and LeSuer (72). The pharmacologic properties were investigated by Lands *et al.*

furthered the pharmacologic studies and found that clinically it was moderately effective only in high doses. The incidence and degree of the side reactions were less than those with most other antihistaminic drugs.

Pyrrolazote.—Closely related to 3015RP, this compound, 10-(β-pyrrolidinoethyl)-phenothiazine, was synthesized by Reid and co-workers (436). The pharmacology of this compound was studied by Vander Brook

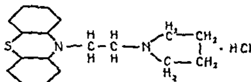


FIG. 14—Pyrrolazote

et al. (552), who found it as effective as Pyribenzamine in antagonizing the action of histamine in animals and decidedly less toxic. Clinically, this drug was tested by us and found to have good clinical potency, giving symptomatic relief in 63 per cent of hay fever patients.

194B (White).—This drug, N,N-dimethyl-N′-2-thiazolyl-N′-p-methoxybenzyl-ethylenediamine, was described by Sondern and Breivogel (509). Pharmacologically, it was found to be a relatively potent antihistamine

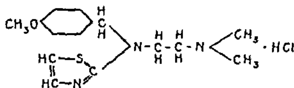


FIG. 15—194B (White)

Moore (351) presented studies before the Federation of American Societies for Experimental Biology in 1945. These data and those of Wells *et al.* (569) and others indicated the effectiveness of Benadryl in antagonizing

FIG. 19—Benadryl.

the effects of histamine in experimental animals. The clinical efficiency of the drug was discussed in a symposium (392) on Benadryl and in articles such as that of McGavack *et al.* (366) wherein it was reported to be effective for many allergic conditions

Decapryn—Sperber and co-workers (512) synthesized this compound which can be known chemically as α-dimethylaminoethoxy - α - 2 - pyridyl-ethyl-benzene.

FIG. 20—Decapryn.

Brown and Werner (61, 62) studied the pharmacologic and antihistamine properties of this drug. Clinically, it was shown to be effective in treating hay fever, although it has a decided sedative effect (183)

MONAMINES

Trimeton—Although the synthesis of this compound, 1-phenyl-1-(2-pyridyl)-3-dimethylaminopro-

(321), who found it to be a highly active antagonist of histamine of about the same order as Pyribenzamine. It did not appear to be significantly more toxic than the other structurally similar compounds (274, 321). No published data are available on the clinical efficacy of this drug.

Ethanolamine Derivatives

929F.—This is the parent instigator of the antihistamines, known as 2-isopropyl-5-methylphenoxyethyldiethylamine (thymoxyethyldiethylamine). It was first

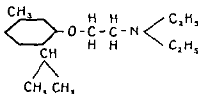


Fig. 18—929F.

synthesized by Einhorn and Rotlauf (148) in 1911 and was among those which Fourneau and Bovet (195, 196) studied in their researches for new antimalarials. Although having some antihistaminic activity (517), its toxicity for both animals and man precluded clinical use.

Benadryl.—Rieveschl and Huber (445) synthesized β-dimethylaminoethylbenzohydryl ether (diphenhydramine) in 1945, thus making it the first antihistamine prepared in this country. Rieveschl, in addition, presented pharmacologic data on Benadryl before the 1945 A.A.A.S. Symposium at Gibson Island, Maryland. Wells and Morris (568), Ellis (152) and Loew, Kaiser and

small doses but that with larger doses the same objections are found as with the other antihistamines.

Miscellaneous Compounds

Antistine.—Meier and Bucher (393) reported the early pharmacologic, including antihistaminic, studies on this compound, 2-(N-benzylanilinomethyl)-imidazoline,

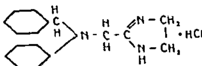


Fig. 23.—Antistine

the synthesis of which was carried out at Ciba, Switzerland. Antistine possesses the usual antihistaminic effects, but our clinical experience indicates that it is one of the less potent of the available drugs.

Thephorin.—Wenner and Plati of the Hoffmann-LaRoche laboratories prepared this compound, 2-methyl-

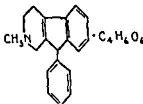


Fig. 24.—Thephorin.

9-phenyl-2,3,4,9-tetrahydro-1-pyridindene. Lehmann (330), who determined its pharmacologic properties, found it had greater potency than Benadryl but less than

pane, has not yet been published by Schering in whose laboratories it was prepared, LaBelle and Tislow (317)

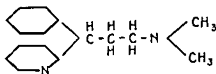


Fig 21 —Trimeton.

described its potency, toxicity and pharmacologic properties, including its antihistamine efficiency. Brown (63) found it to be clinically effective.

Chlor-Trimeton.—Also synthesized by Schering, this chlorine derivative of Trimeton, called 1-p-chlorophenyl-1-(2-pyridyl)-3-dimethylaminopropane, was found to be an effective antihistamine (538) Halogenation of the benzene ring in Trimeton increased the

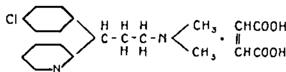


Fig 22 —Chlor-Trimeton.

"therapeutic index" in animals from four to 50 (Pyribenzamine = 1) without apparent change in toxicity, according to Tislow *et al.* (538). Our clinical experiences and those of Eisenstadt (149) in a published report indicated that the drug is clinically effective in

bases Using essentially a similar method, Glazko and co-workers (228–230) followed the course of injected Benadryl in animals. They found that after a subcutaneous injection the highest concentration was in the lung, followed by the spleen, kidney, brain, liver and muscle. The concentration reached a peak in about one hour and fell rapidly to normal within six hours. A small amount of unaltered Benadryl, as well as nonbasic metabolic products, determined by radioactive assay technics, was found in the urine. The liver was indicated as the chief site of degradation

Snyder *et al.* (508) indicated that in rats 7–36 per cent of intravenously or orally administered Decapryn was excreted in the urine within 24 hours. No Decapryn was subsequently found in the tissues. The drug was identified by the ultraviolet absorption wave, antihistaminic effects and isolation as the hydrochloride or reineckate

Pyribenzamine was found by Way and Dailey (559) to be rapidly and completely absorbed from the gastrointestinal tract of the rat within four hours Highest concentrations were present in the lungs, with high concentrations found also in the liver, kidneys and spleen. This tissue Pyribenzamine was no longer detectable after 24 hours The appreciably high concentration found in the brain was thought to be a possible explanation of the toxic effects of the drug. Using 50–100 mg. oral doses, Way and Dailey observed that less than 1 per cent was excreted in the urine in human subjects after 15–24 hours Following alkaline hydrolysis of the urine, an eightfold increase was found, substantiating Perlman's

Pyribenzamine in protecting guinea pigs against histamine. Thephorin was found to be effective in allergic and other dermatoses by Kesten and Sheard (309), and Criep and Aaron (109) indicated that it was moderately effective in nasal allergy.

Chlorcyclizine (Di-Paralene, Perazil).—This drug, N-(p-chlorobenzhydryl)-N′-methyl-piperazine, was synthesized almost simultaneously by Abbott Laboratories and Burroughs Wellcome. The pharmacologic studies

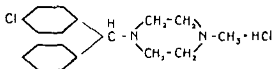


FIG. 25—Chlorcyclizine (Di-Paralene, Perazil).

from these laboratories (79, 470) indicated that it was an effective antihistamine Our (179) clinical studies have shown that its chief advantage is the tendency to prolonged action.

Distribution and Metabolism

Relatively little work has appeared on the distribution of the antihistamines in the tissues following administration and subsequent metabolism. Early in the history of the antihistamines, Gelvin and McGavack (225) found that the concentration of Benadryl in the cerebrospinal fluid was comparable to that in the blood after from 18 to 36 days of treatment with from 100 to 400 mg. daily. Their method of determination, however, was nonspecific and was one used to identify organic

bases. Using essentially a similar method, Glazko and co-workers (228–230) followed the course of injected Benadryl in animals. They found that after a subcutaneous injection the highest concentration was in the lung, followed by the spleen, kidney, brain, liver and muscle. The concentration reached a peak in about one hour and fell rapidly to normal within six hours. A small amount of unaltered Benadryl, as well as nonbasic metabolic products, determined by radioactive assay technics, was found in the urine. The liver was indicated as the chief site of degradation.

Snyder *et al.* (508) indicated that in rats 7–36 per cent of intravenously or orally administered Decapryn was excreted in the urine within 24 hours No Decapryn was subsequently found in the tissues The drug was identified by the ultraviolet absorption wave, antihistaminic effects and isolation as the hydrochloride or reineckate

Pyribenzamine was found by Way and Dailey (559) to be rapidly and completely absorbed from the gastrointestinal tract of the rat within four hours Highest concentrations were present in the lungs, with high concentrations found also in the liver, kidneys and spleen. This tissue Pyribenzamine was no longer detectable after 24 hours. The appreciably high concentration found in the brain was thought to be a possible explanation of the toxic effects of the drug. Using 50–100 mg. oral doses, Way and Dailey observed that less than 1 per cent was excreted in the urine in human subjects after 15–24 hours Following alkaline hydrolysis of the urine, an eightfold increase was found, substantiating Perlman's

Pyribenzamine in protecting guinea pigs against histamine. Thephorin was found to be effective in allergic and other dermatoses by Kesten and Sheard (309), and Criep and Aaron (109) indicated that it was moderately effective in nasal allergy.

Chlorcyclizine (Di-Paralene, Perazil).—This drug, N-(p-chlorobenzhydryl)-N'-methyl-piperazine, was synthesized almost simultaneously by Abbott Laboratories and Burroughs Wellcome. The pharmacologic studies

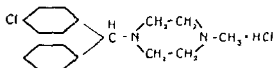


FIG 25—Chlorcyclizine (Di-Paralene, Perazil)

from these laboratories (79, 470) indicated that it was an effective antihistamine. Our (179) clinical studies have shown that its chief advantage is the tendency to prolonged action

Distribution and Metabolism

Relatively little work has appeared on the distribution of the antihistamines in the tissues following administration and subsequent metabolism. Early in the history of the antihistamines, Gelvin and McGavack (225) found that the concentration of Benadryl in the cerebrospinal fluid was comparable to that in the blood after from 18 to 36 days of treatment with from 100 to 400 mg. daily. Their method of determination, however, was nonspecific and was one used to identify organic

bases. Using essentially a similar method, Glazko and co-workers (228–230) followed the course of injected Benadryl in animals. They found that after a subcutaneous injection the highest concentration was in the lung, followed by the spleen, kidney, brain, liver and muscle. The concentration reached a peak in about one hour and fell rapidly to normal within six hours. A small amount of unaltered Benadryl, as well as nonbasic metabolic products, determined by radioactive assay technics, was found in the urine. The liver was indicated as the chief site of degradation.

Snyder *et al.* (508) indicated that in rats 7–36 per cent of intravenously or orally administered Decapryn was excreted in the urine within 24 hours. No Decapryn was subsequently found in the tissues. The drug was identified by the ultraviolet absorption wave, antihistaminic effects and isolation as the hydrochloride or reineckate

Pyribenzamine was found by Way and Dailey (559) to be rapidly and completely absorbed from the gastrointestinal tract of the rat within four hours Highest concentrations were present in the lungs, with high concentrations found also in the liver, kidneys and spleen. This tissue Pyribenzamine was no longer detectable after 24 hours. The appreciably high concentration found in the brain was thought to be a possible explanation of the toxic effects of the drug Using 50–100 mg oral doses, Way and Dailey observed that less than 1 per cent was excreted in the urine in human subjects after 15–24 hours. Following alkaline hydrolysis of the urine, an eightfold increase was found, substantiating Perlman's

(421) observation that about 10 per cent of antihistamine drugs is excreted in a conjugate form. The liver was also found to be important in the metabolism of Pyribenzamine.

Detection and Determination

Methods for the detection and quantitative determination of the antihistaminic drugs have suffered because of the nonspecificity of the reaction For this reason, the technics described essentially deal with the pure, isolated drugs and describe color reactions or crystal formation. Thus, Keenan (303) has described the crystals of the chlorplatinate of Benadryl and Pyribenzamine Haley and his associates (239, 242–245, 303) in a lengthy series, have described the reactions of virtually all the antihistamines with the common alkaloidal, colorimetric and precipitation reagents Although they find that certain of the color reactions can be used as a means of differentiation for some of the antihistamines, the best procedure seems to be optical crystallographic methods

Traub, Friedemann and Landstadt (540) suggested that the suppression of the action of a given concentration of histamine on the skin capillaries of the rabbit could be utilized as a quantitative means of assaying the histamine antagonists. A spectrophotometric assay method was applied to pyranisamine maleate by Anderson and co-workers (11) who indicated that this technic could be applied to elixirs, tablets, parenteral solutions and the like. Benadryl was quantitated by Dill and Glazko (131) from an ethylenedichloride extract

by the methyl orange technic used for organic bases. Pyridine-containing antihistamines were quantitated by Perlman (421) and Jones and Brady (290), utilizing the development of a fluorescing substance found by the actions of cyanogen bromide on the antihistamine. Perlman, estimating the reaction products in the fluorophotometer, noted about 10 per cent recovery of the drugs in a conjugated form in the urine, whereas Jones and Brady, by colorimetric estimation, indicated that more than 85 per cent of an administered dose of Pyribenzamine could be recovered. The results of Perlman are more in keeping with those reported by Way and Dailey (559).

CHAPTER 3

The Pharmacology of the Antihistamines

PHARMACOLOGY OF HISTAMINE

IT APPEARS RELEVANT to present a short survey of the physiology of histamine before entering into a discourse of the agents which negate or alter many of its actions. The chief pharmacologic actions of histamine on the body involve the cardiovascular, respiratory, gastrointestinal and urogenital systems. The response produced by these systems is due chiefly to changes in contractility of the smooth muscle constituents of the tissues comprising the systems. Certain effects are due to stimulation of various glands of external secretion Still other effects are the result of changes in the permeability of capillaries

Cardiovascular system.—Histamine is a powerful dilator of capillaries, an action which is direct on the contractile mechanism, independent of innervation and uninfluenced by blocking drugs such as atropine. Large doses are followed by a precipitous fall in pressure which

may be pronounced and persistent, if not fatal, partly because there is a striking increase in vessel wall permeability, so that there is a loss of plasma protein and fluid into the extracellular areas, and because there is stagnation of blood within the vastly enlarged capillary bed. In the skin, these cause a rise in the surface temperature and a reddening. The intradermal injection results in a local reaction, similar to the triple response of various types of cutaneous stimuli and characterized by (1) a local red area resulting from direct contact of the capillaries with the drug, (2) a diffuse flare due to dilatation of surrounding arterioles by local axon reflexes and (3) ultimately a wheal or area of edema due to transudation of fluid by virtue of the increased permeability.

Excised arteries are constricted by histamine in most species. Pulmonary vessels are constricted in lung sections and apparently even in intact animals, for the pressure in the pulmonary artery rises and the volume of the lung diminishes even when the pressure in the systemic arteries is unchanged.

Abramson and Engel (5) have stressed the activity of the minute cutaneous lymphatics of man in the mechanism of the spread of histamine wheals, which form not so much by diffusion of histamine through the tissues as by the convection of it by the minute lymphatics. At some distance from the original injection site, histamine escapes from the lymphatics into the tissues to act on the blood vessels. Some of it may be taken up again into the lymph stream and transported a little farther through these channels, to escape once more

and act on the tissues at a still more distant site.

Moderate amounts of histamine have little or no effect on the heart. In man, continuous infusion of histamine at a rate of 0.02–0.04 mg. per minute usually produces an increase in heart rate and cardiac output which is due to compensatory reflex responses and not to direct cardiac stimulation. Essex and co-workers (161) have reported that the drug invariably increases the rate of coronary blood flow Electrocardiographic changes which may be seen are often the result of high toxic concentrations weakening the muscle and producing conduction disturbances. There is usually no clinical or electrocardiographic evidence of permanent cardiac damage.

Digestive system.—Histamine has a stimulating action on the musculature of the gastrointestinal tract of most animals, the rabbit being a notable exception. In unanesthetized dogs and cats the intestinal tonus is greatly increased. In most anesthetized animals intravenous injection usually causes marked stimulation, which is diminished but not abolished by atropine.

Histamine is the most potent known excitant of gastric secretion This action is independent of innervation, and amounts which have little or no effect on blood pressure are effective.

Histamine also has a slight stimulating action on salivary, pancreatic, intestinal and lacrimal secretions, but the action is relatively brief in duration and the mechanism is unknown

Uterus.—One of the most characteristic actions of histamine is the powerful contraction of the isolated or

intact uterus. This effect on the excised guinea pig uterus can be detected in a dilution of 1:150,000,000. The uteri of cats and rabbits are less sensitive, and the uterus of the rat is relaxed. The stimulating action seems to be a direct one in the myometrium since it occurs in denervated tissues.

Lungs.—Histamine is a powerful activator of bronchiolar musculature. The action is independent of nerves and is usually unaltered by atropine. Sensitivity reactions vary with the species of animal. Death by asphyxiation, chiefly as a result of bronchiolar constriction, may occur in guinea pigs with doses as small as 0 1 mg The violent dyspnea is only partly caused by obstruction of the bronchioles through spasm of the muscles; congestion and edema of the mucosa also play an important part. The bronchiolar spasm is antagonized by epinephrine and atropine

Miscellaneous effects.—These effects include activation of the excised ureter, dilatation of the pupil in dogs and cats and constriction in the rabbit, decrease in urine formation, variable effects on the cerebrospinal fluid pressure, etc

PHARMACODYNAMICS OF ANTIHISTAMINES

Interest in antihistaminic drugs is related to their use as (1) pharmacologic tools for differentiating between the effects of histamine and those due to other agents, (2) therapeutic agents to alleviate symptoms due to histamine and (3) diagnostic agents to aid in proving or disproving that symptomatology is referable to histamine or to other causes (348). The use of the anti-

histamines in elucidating these numerous problems obviously requires an adequate knowledge of their pharmacologic and toxicologic properties, mode of action, degree of specificity and, in the absence of absolute specificity, a due consideration of other than antihistaminic action. The following, then, is a somewhat detailed discussion of pharmacologic action and toxicity.

Doses of antihistaminic compounds commonly used in animals do not exert a decided effect on respiration, and the clinical literature contains no indication that doses recommended for therapeutic use in man have any effect on respiration (174, 365). An increased rate and amplitude of respiration followed intravenous administration of some of the drugs in anesthetized animals, and the persistence, in general, was concurrent with a normal or slightly increased level of arterial blood pressure. Respiratory stimulation has also been noticed in unanesthetized animals after large oral or parenteral doses of antihistamines (247, 348, 389). Such stimulation usually preceded or was concomitant with pronounced excitability, tremors and convulsions.

Hypotension may result from rapid intravenous injection of the antihistamines. Hypotension, however, was minor in degree, absent or replaced by a slight hypertension which persisted for several minutes when these drugs were administered slowly or by other routes (247, 353, 502, 514, 569). The exact cause of the hypotension or hypertension has not been determined. Since the hypertension persisted for only a few minutes, it scarcely could be related to other actions of the drugs, such as antagonism of histamine which was demon-

stable for several hours Doses of antihistamines which are therapeutically effective in allergic disease do not raise blood pressure (174, 224, 365). This indicates that the antihistaminic compounds lack the pressor properties possessed by epinephrine and its congeners.

Pyribenzamine usually produces a slight fall in the cerebrospinal fluid pressure (321). Antistine has no such effect

The majority of antihistamines exert some local anesthetic action (247, 351). Local anesthetic action should be considered when interpreting effects of antihistaminic drugs on vascular and cutaneous responses in which axon and other reflexes are involved. Such action is possibly related to antipruritic effects and production of cutaneous analgesia about which more will be found in Chapters 7 and 8. Halpern (259, 260) made some attempt to quantitate the local anesthetic action and concluded that this action is not responsible for nor does it parallel the antihistaminic effects. Yonkman and co-workers (585) observed a loss of wink reflex in the rabbit following the local instillation of Antistine, and both this drug and Pyribenzamine produced anesthesia of the conjunctiva in man. Sheldon and his group (498), however, stated that Benadryl, Decapryn, Antistine and Pyribenzamine, in proper therapeutic doses, produced no apparent significant depression of the corneal reflex in rabbits when these drugs were given intravenously, orally or by ophthalmic application Hyperesthesia could occur

In animals, antihistamines do not induce sedation, hypnosis or depressant effects. Toxic doses of all antihis-

taminic drugs, with the exception of quarternary derivatives of Benadryl (576), rather stimulate the central nervous system, evidenced by hyperexcitability, tremors and convulsions. Neither excitation nor sedation is seen in smaller doses. For these reasons it occurred to Winter (578) that these drugs might show a potentiating effect on the sedative action of barbiturates and that by this means the sedative attributes of the antihistamines could be measured. Experiments on mice sedated with Evipal showed that the mean waking time was prolonged about 10 per cent by Pyribenzamine and Neo-Antergan and about 40 per cent by 3277RP and Benadryl These results appear to be correlated with the reported incidence of sedation in man. In addition to the sedation which many of these compounds produce in man, dizziness sometimes follows administration of therapeutic doses The sedation is unpredictable, variable in degree from person to person and constitutes a side effect which has been encountered frequently. It is discussed more completely in Chapters 9 and 10.

Untoward reactions in man which result from direct or indirect actions of antihistaminic drugs on the gastrointestinal tract include gastric distress, nausea, emesis, colic and diarrhea. Such reactions are less frequently encountered with Benadryl (162, 334) which usually exerts a slight degree of antispasmodic action In fact, Benadryl was found to have an antiemetic effect in apomorphine-induced vomiting in dogs (82).

Antihistaminic drugs are absorbed rapidly following oral administration and parenteral injection. The usual experimental and therapeutic doses exert an antihista-

minic effect in animals and man for two to six hours. No information is available concerning effective blood levels A discussion of the mode and rate of destruction or elimination appears in the preceding chapter.

ANTAGONISM OF HISTAMINE

Bronchioles.—The usual procedure which has been adopted in the screening and evaluation of the antihistaminic drugs is to determine their ability to prevent the bronchoconstriction which is so conspicuous in guinea pigs exposed to histamine or during anaphylaxis. The method frequently used is that of Loew, Kaiser and Moore (351) which, essentially, is a modification of that used by Kallos and Pagel (295) and others (247). It consists of determining the minimum effective dose of a given drug which significantly reduces the mortality rate of guinea pigs exposed to a lethal dose of an atomized histamine solution The advantage of this technic is that a set of conditions can be sufficiently standardized to yield a degree of consistency in the incidence of asphyxial deaths referable to histamine-induced bronchoconstriction in untreated guinea pigs, thereby permitting a fairly reliable index of the minimum effective dose. With previous methods a reliable comparison of the relative effectiveness of various drugs could not be made, since various investigators used different technics and often failed to include a standard or reference compound.

By such a technic virtually all the antihistamines used clinically were shown to possess an action antagonistic to histamine aerosol in that they either prevented or di-

minished the degree of bronchoconstriction. And, too, by this technic experimental compounds were screened for their antihistaminic capacities. Thus, the early reports (51, 514, 517) that 929F and 1571F could diminish the bronchoconstrictive effects of histamine in guinea pigs were confirmed by other investigators (247, 351, 352, 465, 574). Antergan (247, 248) and 2325RP were shown to be more effective. In rapid succession, the drugs with which we are now familiar clinically were found to be capable of diminishing the action of histamine. Although by no means complete, the following listing gives some of the early experiences with each drug. Neo-Antergan (49), Benadryl and related compounds (351, 352, 353, 502), Pyribenzamine (383, 390), Antistine (393), Hetramine (190), 3015RP and 3227RP (Phenergan) (253, 257), Histadyl (Thenylene) (159, 327, 345, 469), chlorothen (Tagathen) (345), Diatrin (314), Neohetramine (32, 437), Pyrrolazote (552), Decapryn (61, 62), Trimeton (317), Thephorin (330), p-fluorobenzyl-DPE (346, 554), Chlor-Trimeton (538), chlorcyclizine (Di-Paralene, Perazil) (79, 470), Thenfadil (321) and 194B (White) (187). In addition to the effectiveness of these drugs on the bronchospasm produced by histamine aerosol, each of them was capable of antagonizing the constriction induced by intravenous injection of histamine.

Despite the apparent constancy of results of the aerosol technic it becomes obvious that any attempt to compare the effectiveness of different drugs suffers partly because of individual variation in technic and individual variation of different investigators. Then, too, most in-

vestigators have been satisfied with a comparison of their compound with one or two others (206, 502, 577). In order to assess the relative potency of the antihistamines on some comparative basis, we realized the necessity for a comparative evaluation of the compounds with the same technics and in the hands of one group of investigators In assessing the potency of a long series of antihistamines, Feinberg *et al* (187) used the following technic. Guinea pigs were injected with varying amounts of the compound intraperitoneally (usually 0.1 and 1.0 mg. per kg.) 30 minutes before the animals were subjected to histamine. Histamine was administered in two ways (1) as an aerosol from a solution of a concentration of 0.5 mg per ml. in terms of the free base and (2) intravenously with one MLD_{100} (the minimum dose found 100 per cent fatal for a control series of guinea pigs). In another series of experiments, pretreatment with the antihistamine consisted in subjecting the animals for five minutes to an aerosol of the antihistamine, in varying concentrations, before exposure to histamine aerosol The results showed that the various types of experiments were in agreement as to the degree of potency of a compound and that the potency of a given compound could be compared with that of another Thus, for example, Antistine and Neohetramine showed not only a low effectiveness against histamine shock but also against the action of histamine aerosol. Such compounds as Pyribenzamine, Chlor-Trimeton, Neo-Antergan, Hisradyl (Thenylene), Tagathen and p-fluorobenzyl-DPE displayed high effectiveness in all technics. It must be noted, however, that there was no absolute

minished the degree of bronchoconstriction. And, too, by this technic experimental compounds were screened for their antihistaminic capacities. Thus, the early reports (51, 514, 517) that 929F and 1571F could diminish the bronchoconstrictive effects of histamine in guinea pigs were confirmed by other investigators (247, 351, 352, 465, 574). Antergan (247, 248) and 2325RP were shown to be more effective. In rapid succession, the drugs with which we are now familiar clinically were found to be capable of diminishing the action of histamine. Although by no means complete, the following listing gives some of the early experiences with each drug. Neo-Antergan (49), Benadryl and related compounds (351, 352, 353, 502), Pyribenzamine (383, 390), *Antistine* (393), *Hetramine* (190), 3015RP and 3227RP (Phenergan) (253, 257), Histadyl (Thenylene) (159, 327, 345, 469), chlorothen (Tagathen) (345), Diatrin (314), Neohetramine (32, 437), Pyrrolazote (552), Decapryn (61, 62), Trimeton (317), Thephorin (330), p-fluorobenzyl-DPE (346, 554), Chlor-Trimeton (538), chlorcyclizine (Di-Paralene, Perazil) (79, 470), Thenfadil (321) and 194B (White) (187). In addition to the effectiveness of these drugs on the bronchospasm produced by histamine aerosol, each of them was capable of antagonizing the constriction induced by intravenous injection of histamine.

Despite the apparent constancy of results of the aerosol technic it becomes obvious that any attempt to compare the effectiveness of different drugs suffers partly because of individual variation in technic and individual variation of different investigators. Then, too, most in-

duced intestinal spasm was diminished by Antistine (393) and Neo-Antergan (502). Pyribenzamine in a dilution of 1:50,000,000 was sufficient to prevent the spasmogenic action of histamine (383). Virtually all the antihistamines which were subsequently synthesized showed the capacity to prevent this action of histamine, although not all the data are of a quantitative nature al-

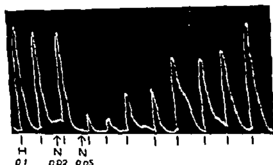


FIG. 26—Action of an antihistamine, *N*, on guinea pig ileum All doses indicated in micrograms, in bath volume of 20 ml Unlabeled vertical lines are all 0.1 µg. histamine (as base) *N*, Neo-Antergan.

lowing for comparisons (319). In evaluating a given antihistamine by this technic, Chen *et al.* (83) have stressed the need for making the comparison against a standard on the same ileal strip.

Suppression of the spasmogenic action of acetylcholine and barium was also accomplished by 929F and 1571F when sufficient doses were used (247, 353, 576). Halpern (247) found that several hundred times the concentration of 2325RP and Antergan was needed to

parallelism between the findings for any two compounds with all technics.

We realize that some of our findings are in disagreement with those of other investigators, particularly with reference to histamine shock. These reports, such as those of Staub (514) and Brown and Werner (62), usually were based on the number of lethal doses of histamine against which the animals were protected after a larger dose of the antihistaminic compound. Nevertheless, our work and that of others (345, 577) indicates that a determination of the amount of the drug required to protect against one lethal dose of histamine approaches more closely the clinical potency of the drug than the findings obtained by the older methods.

Shock caused by histamine injected intravenously was prevented in guinea pigs by subcutaneous implantation of Pyribenzamine in beeswax (304). On removing the pellet, the animals responded to histamine in a manner similar to that of the controls.

Intestinal muscle.—Staub (514) reported that 929F and 1571F in a dilution of 1 2,000,000 to 1:10,000,000 prevented histamine from contracting isolated guinea pig ileum. Halpern (247) compared 1571F, 2325RP and Antergan for their antispasmogenic action. The last drug was the most effective. Other direct comparisons of the antihistamine action of several drugs on intestinal muscle were made by Loew *et al.* (353), who found that the spasm induced with histamine diphosphate was reduced by 1571F and Benadryl, whereas antispasmodics such as atropine, Pavatrine and Trasentin were only effective in much lower concentrations. Histamine-in-

which may reveal differences in the potency of these drugs against this action of histamine.

The variable response of the cerebrospinal fluid pressure to histamine was antagonized by Pyribenzamine and Antistine (106).

Capillary permeability and cutaneous reactions.—Many diverse stimuli, such as thermal, chemical, mechanical, etc., can elicit an inflammatory reaction. The question of the participation of histamine in these reactions is important, because histamine has been implicated in the flare and wheal response of the local inflammatory reaction The measurement of the cutaneous response to histamine per se and the effects of the antihistaminic drugs on these cutaneous reactions have been studied in a precise manner especially by us (358) and will be discussed in Chapter 5. The discussion in this section will therefore be restricted to nonquantitative, localized responses, not all of which are mediated by histamine release.

The extravasation of a dye, such as trypan blue, and its localized accumulation which usually follows the intradermal injection of histamine has been used as a measure of increased capillary permeability in animals. Benadryl (323), Neo-Antergan (323) and Pyribenzamine (439) were found to diminish or annul this effect. Benadryl (323) failed to affect the spread of the dye induced by other agents such as trypsin (571), snake venom, staphylococcus toxin, heparin, Pontocaine, codeine and horse serum in nonsensitized rabbits. Nontoxic doses of Pyribenzamine or Benadryl when dropped slowly on three-day chick embryos before or concomi-

antagonize the spasmogenic action of acetylcholine and barium than was required for histamine antagonism *Pyribenzamine* (383) *and Neo-Antergan* (129) weakly antagonized the spasmogenic action of acetylcholine.

The antihistamines, in general, show no striking antispasmodic action on isolated rabbit intestine, such as diminishing the tonus or the spontaneous motility. Data are available for 929F and 1571F (514), 2325RP (247), Neo-Antergan and Pyribenzamine (129, 502). Benadryl was found to decrease the tonus and motility of the rabbit intestine, whereas Neo-Antergan and Pyribenzamine stimulated intestinal and uterine activity when injected intravenously in anesthetized dogs (502). *Most of the antihistamines, then, do not prevent spasm* or exert a prominent relaxing effect on intestinal muscle except under conditions in which histamine has produced increased tonus, hypermotility or spasm.

Uterine muscle.—Limited data (129, 247, 383, 514) are available for some of the antihistamines which seem to indicate that probably all are capable of contracting uterine muscle and that all antagonize the oxytocic action of histamine.

Arterial blood pressure.—The depressor action of histamine in anesthetized dogs was found to be diminished by the antihistamines tested (48, 49, 353, 502, 568, 569, 583). These drugs appeared to possess equal potency with regard to antagonizing the depressor effects of identical doses of histamine in dogs even though their ability to antagonize the bronchoconstrictive action of histamine in guinea pigs varied widely. It is possible that quantitative data *can be obtained by other technics*

which may reveal differences in the potency of these drugs against this action of histamine

The variable response of the cerebrospinal fluid pressure to histamine was antagonized by Pyribenzamine and Antistine (106).

Capillary permeability and cutaneous reactions.—Many diverse stimuli, such as thermal, chemical, mechanical, etc, can elicit an inflammatory reaction. The question of the participation of histamine in these reactions is important, because histamine has been implicated in the flare and wheal response of the local inflammatory reaction. The measurement of the cutaneous response to histamine per se and the effects of the antihistaminic drugs on these cutaneous reactions have been studied in a precise manner especially by us (358) and will be discussed in Chapter 5. The discussion in this section will therefore be restricted to nonquantitative, localized responses, not all of which are mediated by histamine release.

The extravasation of a dye, such as trypan blue, and its localized accumulation which usually follows the intradermal injection of histamine has been used as a measure of increased capillary permeability in animals. Benadryl (323), Neo-Antergan (323) and Pyribenzamine (439) were found to diminish or annul this effect. Benadryl (323) failed to affect the spread of the dye induced by other agents such as trypsin (571), snake venom, staphylococcus toxin, heparin, Pontocaine, codeine and horse serum in nonsensitized rabbits Nontoxic doses of Pyribenzamine or Benadryl when dropped slowly on three-day chick embryos before or concomi-

tant with the administration of normal rabbit serum failed to prevent the vascular phenomenon (405). Rigdon (446) observed that prior injections of Thenylene or Pyrrolazote had no effect on the intensity of edema produced by the application of xylene to the skin of animals. The trypan blue concentration was also not altered. These data suggest that the action of the antihistamines on capillary permeability is limited to an antagonism of histamine and that the increase of permeability due to trypsin, toxins, serum, etc., is through a mechanism which does not involve histamine. Antihistamines probably diminish whealing by preventing histamine from increasing capillary permeability or by acting directly to decrease permeability (348). If the action is direct, the antihistaminic drugs should diminish increased capillary permeability caused by a variety of agents which do not contain or liberate histamine.

Haley and Harris (240) have explained the decrease in diffusion of trypan blue on the basis of the vasoconstrictor action of the antihistamines. These drugs not only negate the vasodilator action of histamine on the precapillary sphincters of the mammalian capillary bed but also have a vasoconstrictor effect. These authors also used this explanation to account for the reduction of the wheal and flare reactions in human beings as well as the tuberculin skin reaction. The latter question will be taken up in later chapters.

Allied to the vasoconstrictor action of the antihistamines is the observation of Halpern (251) that large doses caused the dissemination of localized infection in control animals, with the production of septic infec-

tions. Friedlaender and Feinberg (204) noted that the local application of Benadryl would reduce the wheal and flare response produced by a scratch test to codeine sulfate in man. However, Loew (348) has pointed out that a 5 per cent solution of Benadryl would exert local anesthetic action and thus affect axon reflexes concerned in flare reactions.

A novel and interesting approach to the measure of changes in capillary permeability was utilized by Bukantz and Dammin (68). Histamine injected intradermally into the skin of man and dogs increased the capillary permeability of intradermal fluorescein as measured under ultraviolet light by the dermofluorometer.

With respect to the use of the flare and wheal response to histamine and thereby its use in quantitation of antihistaminic drugs, Darsie and co-workers (120) pointed out that the proper selection of laboratory animals is of the utmost importance in dermatologic experiments involving a local skin reaction. For example, guinea pigs, rabbits and cats showed no whealing response to an intracutaneous injection of histamine, while dogs, monkeys and man gave positive results. In addition, when the concentration of histamine diphosphate was below 0.001 per cent the diameter of the wheal was no longer a reliable index of the action of histamine. The wheals produced by low concentrations of histamine showed greater variation in size than did those produced by the higher concentrations.

Because of the concept that histamine release is the cause of shock in burns, Gunnar and Weeks (237) investigated the effect of Pyribenzamine on the burn

tant with the administration of normal rabbit serum failed to prevent the vascular phenomenon (405). Rigdon (446) observed that prior injections of Thenylene or Pyrrolazote had no effect on the intensity of edema produced by the application of xylene to the skin of animals. The trypan blue concentration was also not altered. These data suggest that the action of the antihistamines on capillary permeability is limited to an antagonism of histamine and that the increase of permeability due to trypsin, toxins, serum, etc., is through a mechanism which does not involve histamine. Antihistamines probably diminish whealing by preventing histamine from increasing capillary permeability or by acting directly to decrease permeability (348). If the action is direct, the antihistaminic drugs should diminish increased capillary permeability caused by a variety of agents which do not contain or liberate histamine.

Haley and Harris (240) have explained the decrease in diffusion of trypan blue on the basis of the vasoconstrictor action of the antihistamines. These drugs not only negate the vasodilator action of histamine on the precapillary sphincters of the mammalian capillary bed but also have a vasoconstrictor effect. These authors also used this explanation to account for the reduction of the wheal and flare reactions in human beings as well as the tuberculin skin reaction. The latter question will be taken up in later chapters.

Allied to the vasoconstrictor action of the antihistamines is the observation of Halpern (251) that large doses caused the dissemination of localized infection in control animals, with the production of septic infec-

tions. Friedlaender and Feinberg (204) noted that the local application of Benadryl would reduce the wheal and flare response produced by a scratch test to codeine sulfate in man. However, Loew (348) has pointed out that a 5 per cent solution of Benadryl would exert local anesthetic action and thus affect axon reflexes concerned in flare reactions

A novel and interesting approach to the measure of changes in capillary permeability was utilized by Bukantz and Dammin (68). Histamine injected intradermally into the skin of man and dogs increased the capillary permeability of intradermal fluorescein as measured under ultraviolet light by the dermofluorometer.

With respect to the use of the flare and wheal response to histamine and thereby its use in quantitation of antihistaminic drugs, Darsie and co-workers (120) pointed out that the proper selection of laboratory animals is of the utmost importance in dermatologic experiments involving a local skin reaction. For example, guinea pigs, rabbits and cats showed no whealing response to an intracutaneous injection of histamine, while dogs, monkeys and man gave positive results. In addition, when the concentration of histamine diphosphate was below 0.001 per cent the diameter of the wheal was no longer a reliable index of the action of histamine. The wheals produced by low concentrations of histamine showed greater variation in size than did those produced by the higher concentrations.

Because of the concept that histamine release is the cause of shock in burns, Gunnar and Weeks (237) investigated the effect of Pyribenzamine on the burn

tant with the administration of normal rabbit serum failed to prevent the vascular phenomenon (405). Rigdon (446) observed that prior injections of Thenylene or Pyrrolazote had no effect on the intensity of edema produced by the application of xylene to the skin of animals. The trypan blue concentration was also not altered. These data suggest that the action of the antihistamines on capillary permeability is limited to an antagonism of histamine and that the increase of permeability due to trypsin, toxins, serum, etc., is through a mechanism which does not involve histamine. Antihistamines probably diminish whealing by preventing histamine from increasing capillary permeability or by acting directly to decrease permeability (348). If the action is direct, the antihistaminic drugs should diminish increased capillary permeability caused by a variety of agents which do not contain or liberate histamine.

Haley and Harris (240) have explained the decrease in diffusion of trypan blue on the basis of the vasoconstrictor action of the antihistamines. These drugs not only negate the vasodilator action of histamine on the precapillary sphincters of the mammalian capillary bed but also have a vasoconstrictor effect. These authors also used this explanation to account for the reduction of the wheal and flare reactions in human beings as well as the tuberculin skin reaction. The latter question will be taken up in later chapters.

Allied to the vasoconstrictor action of the antihistamines is the observation of Halpern (251) that large doses caused the dissemination of localized infection in control animals, with the production of septic infec-

Heidenhain gastric pouches, 1571F failed to modify secretion after a food stimulus (46) but in dogs with innervated pouches it inhibited secretion (246). When large single doses of histamine were employed neither drug inhibited secretion (69). The secretory inhibition demonstrated by 1571F was probably not referable to a specific antagonism of histamine since pilocarpine-induced secretion from denervated pouches was also inhibited (46)

Decourt, Rinieri and Sonnet (124) made the observation that in man 2786RP and 2339RP neither provoked gastric secretion nor were capable of suppressing the gastric effect of histamine. The failure of Benadryl to antagonize the secretagogue action of histamine in dogs with various types of pouches (211, 477) has been corroborated (105) Pyribenzamine also failed to antagonize this effect (477). The formation of duodenal and gastric ulcers in dogs which received large amounts of histamine in beeswax was not prevented either by Benadryl (211, 105) or by Tagathen (553).

The available evidence from human and animal experimentation seems to justify the conclusion that none of the antihistamines directly antagonizes the gastric secretagogue action of histamine. Thus, at least one of the prominent effects of histamine was not significantly diminished by the antihistaminic drugs.

Antergan and 2325RP given intravenously were found to augment salivary secretion, according to Halpern (247). Yonkman *et al.* (584) noted that, although the salivary secretion induced by carotid injections of histamine was highly variable, it appeared to

shock. Large doses of Pyribenzamine given intravenously did not affect the onset and progression of the shock symptoms in rabbits. Sevitt (495) arrived at essentially the same conclusions with Benadryl, Antistine and Neo-Antergan in guinea pigs in that there was no alteration of any of the manifestations of the burn. Weeks and Gunnar (560) indicated that the erythema from burns and turpentine was reduced by Pyribenzamine but that *neither the capillary permeability nor the microscopic* picture of acute inflammation was altered.

Ingraham and Wiggers (285) failed to induce beneficial results in hemorrhagic shock in dogs by the use of Benadryl even though the antihistamines diminish the vasopressor action of histamine and its action of increasing capillary permeability. These authors suggested that the liberation of histamine may play no role in the production of the irreversible tissue damage of hemorrhagic shock.

Glandular secretion.—The antagonistic effect that the antihistamines display on the actions of histamine on the vascular system and on smooth muscle seems to indicate that such drugs might inhibit lacrimal, salivary, gastric and pancreatic secretion following stimulation of these glands with histamine.

Loew and Chickering (349) and Hallenbeck (246) found that in dogs the subcutaneous injection of 929F before a subcutaneous injection of histamine actually increased the volume and acidity of secretion over that which was obtained during control periods when only the histamine stimulus was used The secretion may vary depending on the innervation; in dogs with denervated

as Winter (579) observed no effect with Phenergan in rabbits, rats and guinea pigs.

Hyaluronidase is known to increase the spread of allergic epidermal reactions in the guinea pig sensitized to p-phenylenediamine (391). Pretreatment with Pyribenzamine almost completely suppressed the allergic reaction. Antistine as well as Pyribenzamine suppressed the spreading effect of hyaluronidase on subcutaneously injected India ink. Elster, Freeman and Lowry (153) noted that Pyribenzamine and Benadryl inhibited the hematocrit and fluid diffusion effects of intravenous hyaluronidase. They and Moynahan and Watson (402) indicated that the antihistamines had no effect on hyaluronidase in vitro The compounds tested were Pyribenzamine, Neo-Antergan, Benadryl and Antistine

In a series of rabbits in which orthostatic albuminuria was induced, Hamburger *et al.* (262) found that administration of 3277RP eliminated the albuminuria within 30 minutes. They believed that these results favor the concept that albuminuria of this type has to do with capillary permeability of the kidneys. Benadryl was shown by Chen and Clark (81) to have a hyperglycemic effect in rabbits which was in addition to that of epinephrine. Its effect is apparently due to central nervous system stimulation, since it could be inhibited by a depressant (pentobarbital). The simultaneous injection of Pyribenzamine or Antistine and histamine prevented the loosening of the upper layers of the epithelium of the excised bovine cornea (267).

Levitan and Scott (339) observed that Pyribenzamine and Antistine in relatively large doses inhibited the

be diminished or annulled by Pyribenzamine. Lactimation induced with histamine was stated to be definitely suppressed after Pyribenzamine injections. The meager, nonquantitative data which are available do not allow for an opinion concerning the secretagogue action of histamine on lacrimal, salivary and pancreatic glands. Loew (348) has indicated that since histamine-induced gastric secretion was not antagonized, it is possible that histamine acts on secretory cells through some mechanism which differs from that obtaining in endothelial and smooth muscle cells; or, the antihistamines either do not reach or have no affinity for the elements in the secretory cell which react to histamine.

Miscellaneous Antihistaminic Effects

Closely akin to the alteration of capillary permeability by the antihistamines is the question of pulmonary edema produced by epinephrine. Halpern and co-workers (252, 255, 256) have stated that 3277RP injected prior to epinephrine prevented death due to pulmonary edema in all rabbits. Preceding this event there is an initial increase in blood pressure, apnea followed by rapid and difficult respiration, a subsequent fall in blood pressure and frothy blood expectoration. Although these authors realized that an injection of epinephrine in man liberates histamine in the plasma, they observed that Neo-Antergan afforded only partial protection against pulmonary edema while 3300RP, which is closely related to 3277RP, gave none. Neo-Antergan in the hands of Stone and Loew (523) failed to prevent epinephrine pulmonary edema in rabbits, and these authors as well

as Winter (579) observed no effect with Phenergan in rabbits, rats and guinea pigs.

Hyaluronidase is known to increase the spread of allergic epidermal reactions in the guinea pig sensitized to p-phenylenediamine (391). Pretreatment with Pyribenzamine almost completely suppressed the allergic reaction. Antistine as well as Pyribenzamine suppressed the spreading effect of hyaluronidase on subcutaneously injected India ink. Elster, Freeman and Lowry (153) noted that Pyribenzamine and Benadryl inhibited the hematocrit and fluid diffusion effects of intravenous hyaluronidase. They and Moynahan and Watson (402) indicated that the antihistamines had no effect on hyaluronidase in vitro. The compounds tested were Pyribenzamine, Neo Antergan, Benadryl and Antistine.

In a series of rabbits in which orthostatic albuminuria was induced, Hamburger *et al.* (262) found that administration of 3277RP eliminated the albuminuria within 30 minutes. They believed that these results favor the concept that albuminuria of this type has to do with capillary permeability of the kidneys. Benadryl was shown by Chen and Clark (81) to have a hyperglycemic effect in rabbits which was in addition to that of epinephrine. Its effect is apparently due to central nervous system stimulation, since it could be inhibited by a depressant (pentobarbital). The simultaneous injection of Pyribenzamine or Antistine and histamine prevented the loosening of the upper layers of the epithelium of the excised bovine cornea (267).

Levitan and Scott (339) observed that Pyribenzamine and Antistine in relatively large doses inhibited the

be diminished or annulled by Pyribenzamine. Lacrimation induced with histamine was stated to be definitely suppressed after Pyribenzamine injections. The meager, nonquantitative data which are available do not allow for an opinion concerning the secretagogue action of histamine on lacrimal, salivary and pancreatic glands. Loew (348) has indicated that since histamine-induced gastric secretion was not antagonized, it is possible that histamine acts on secretory cells through some mechanism which differs from that obtaining in endothelial and smooth muscle cells; or, the antihistamines either do not reach or have no affinity for the elements in the secretory cell which react to histamine.

Miscellaneous Antihistaminic Effects

Closely akin to the alteration of capillary permeability by the antihistamines is the question of pulmonary edema produced by epinephrine. Halpern and co-workers (252, 255, 256) have stated that 3277RP injected prior to epinephrine prevented death due to pulmonary edema in all rabbits. Preceding this event there is an initial increase in blood pressure, apnea followed by rapid and difficult respiration, a subsequent fall in blood pressure and frothy blood expectoration. Although these authors realized that an injection of epinephrine in man liberates histamine in the plasma, they observed that Neo-Antergan afforded only partial protection against pulmonary edema while 3300RP, which is closely related to 3277RP, gave none. Neo-Antergan in the hands of Stone and Loew (523) failed to prevent epinephrine pulmonary edema in rabbits, and these authors as well

as Winter (579) observed no effect with Phenergan in rabbits, rats and guinea pigs.

Hyaluronidase is known to increase the spread of allergic epidermal reactions in the guinea pig sensitized to p-phenylenediamine (391). Pretreatment with Pyribenzamine almost completely suppressed the allergic reaction Antistine as well as Pyribenzamine suppressed the spreading effect of hyaluronidase on subcutaneously injected India ink. Elster, Freeman and Lowry (153) noted that Pyribenzamine and Benadryl inhibited the hematocrit and fluid diffusion effects of intravenous hyaluronidase. They and Moynahan and Watson (402) indicated that the antihistamines had no effect on hyaluronidase in vitro. The compounds tested were Pyribenzamine, Neo-Antergan, Benadryl and Antistine

In a series of rabbits in which orthostatic albuminuria was induced, Hamburger *et al.* (262) found that administration of 3277RP eliminated the albuminuria within 30 minutes. They believed that these results favor the concept that albuminuria of this type has to do with capillary permeability of the kidneys. Benadryl was shown by Chen and Clark (81) to have a hyperglycemic effect in rabbits which was in addition to that of epinephrine Its effect is apparently due to central nervous system stimulation, since it could be inhibited by a depressant (pentobarbital). The simultaneous injection of Pyribenzamine or Antistine and histamine prevented the loosening of the upper layers of the epithelium of the excised bovine cornea (267)

Levitan and Scott (339) observed that Pyribenzamine and Antistine in relatively large doses inhibited the

development of ventricular fibrillation when epinephrine was given to dogs sensitized to chloroform. The effects were only of short duration and were inconstant. These authors (340) also found that neither Pyribenzamine nor Benadryl would prevent ventricular fibrillation and death resulting from the experimental occlusion of the circumflex branch of the left coronary artery. Emmelin and Muren (154) determined that the antihistamines would specifically antagonize the action of histamine on the adrenal medulla. Antergan, Benadryl, Neo-Antergan and Pyribenzamine when injected into the central stump of the celiac artery caused an output of epinephrine from the suprarenals.

Pyribenzamine inhibited the oxidation of glucose and pyruvate in the anaerobic glycolysis of glucose by mouse brain homogenates (278). The fact that the succinic oxidase and cytochrome oxidase systems were not affected was thought to suggest that the site of inhibition is between the pyridine nucleotides and the cytochrome systems. These effects may explain the hypnotic and local anesthetic action of Pyribenzamine. The antihistaminic drugs were found to have no antibacterial or bacteriostatic activity (60). Antihistamine medication caused an increase in mortality in guinea pigs exposed to x-ray (241).

CHAPTER 4

Antihistamines in Experimental Hypersensitivities

FOLLOWING DISCUSSION of the remarkable specific antagonistic properties of the antihistamines on histamine-induced bronchiolar constriction, intestinal and uterine contraction, cutaneous reactions and increased capillary permeability, etc., in the preceding chapter, our attention now turns to the effects of the antihistamines on experimental phenomena related to clinical allergy. Such a discussion will entail the effects of these drugs on immunologic processes, the end results of which, for the most part, stem from a concomitant release of histamine.

ANAPHYLAXIS IN DIFFERENT SPECIES

We have already seen that the symptoms and reactions to histamine are nearly identical to those occurring in anaphylaxis The reactions to histamine differ from one species to another because different shock organs or tissues give rise to the dominant reaction Correspondingly, the anaphylactic reactions differ from species to species,

but in a given species they are always strikingly similar to histamine reactions.

Thus, in the guinea pig, the most commonly used experimental animal in the study of anaphylaxis, the most characteristic signs and symptoms are those associated with the respiratory tract. Distress appears rapidly: "The hair on the head and back of the neck begins to ruffle. The animal becomes restless, coughs and retches, rubs its nose, and seems to choke. The respirations which were at first increased in frequency become slower and labored and soon the animal is gasping for breath and making tremendous inspiratory efforts. The mucous membranes become cyanotic. The animal defecates and urinates. If the anaphylactic shock is destined to end fatally the animal soon becomes weak and rolls over on its side, gives a few convulsive kicks, gasps and stops breathing" (487). This cycle may be over in five minutes in very severe shock. If the shock is less severe, shivering sets in, followed by recovery and gradual improvement. The blood pressure which rises at first gradually falls in about 10 minutes. Asphyxia is the immediate cause of death. The lungs are markedly inflated owing to constriction of the bronchial musculature. Small hemorrhages are common on the under side of the diaphragm and in the viscera.

Death due to anaphylaxis is not so common in the rabbit, but when it occurs it is usually rapid The animal will lie with legs outstretched or will fall on its side, give a series of convulsive movements and die. The blood pressure and body temperature fall. Pathologically, the pulmonary dilatation found in the guinea pig is absent

and there are no prominent hemorrhages in the splanchnic area, although some congestion of the liver and other viscera may be found. The most characteristic finding is the extreme dilatation of the right side of the heart and the inferior vena cava with blood, apparently caused by constriction of the pulmonary arteries.

In the dog vomiting is so characteristic and severe with profound anaphylaxis that it may be taken as a criterion The vomitus is frothy and mixed with bile; sometimes it is fecal and sometimes, in severest cases, mixed with blood. There is diarrhea mixed with blood. Respiration is quickened and dyspneic, the arterial blood pressure is very low and the heart beat is weak and rapid. The general condition is serious enough for one to believe death imminent, but in reality death in less than two hours is extremely rare. In the dog the liver is greatly congested during shock and most of the observed symptoms are referable to the liver The intense congestion has been explained on the basis of injury to the liver sinusoids and liver cells, allowing transudation of fluid, edema and congestion with red cells and obstruction of the hepatic veins, producing interference with the outflow of blood

Anaphylactic shock is a less stormy event in the mouse. According to McMaster and Kruse (372), soon after the shocking dose is administered a blanching occurs in the ears and feet. This appears regularly and before the reported cyanosis Agitation and hyperexcitability also are early signs. Later the animals scratch themselves, the hair becomes ruffled, respirations become difficult and brief, intermittent convulsions appear. There

is often a froglike posture, with the hind legs extended behind the body (563). Death occurs only after 15–60 minutes, at times after many hours. The lungs show moderate emphysema and the intestine and stomach are congested and hemorrhagic.

PREVENTION OF ANAPHYLACTIC SHOCK

Since histamine is significantly involved in anaphylaxis, the antihistaminic drugs would be expected to be effective in diminishing the anaphylactic reactions in each species. Numerous reports have appeared which indicate that those antihistamines which effectively antagonize the bronchoconstrictive action of histamine are capable of diminishing the severity of anaphylaxis in the guinea pig, in which animal bronchoconstriction is the prominent feature of anaphylaxis. Thus, following the report (195) that certain phenolic ethers had the property of inhibiting or counteracting the action of histamine, Staub and Bovet (517) found that the compound designated as 929F (2-isopropyl-5-methylphenoxyethyldiethylamine), had definite antianaphylactic properties since it protected actively sensitized guinea pigs *against a shocking dose of horse serum. Staub* (514, 516) and others (465) confirmed this effect. Historically, the next drug studied was 1571F (N,N-diethyl-N'-phenyl-N'-ethyl-ethylenediamine) and it, too, was found to possess antihistaminic and antianaphylactic properties (247, 514, 516, 574).

Following these, there were described the antianaphylactic properties of Antergan (247, 344) and 2325RP (*N'-phenyl-N'-ethyl-N-dimethylethylenedi-*

amine (247). Bovet, Horclois and Walthert (49) discussed 2786RP or Neo-Antergan and established its value as an antianaphylactic agent. Many reports (18, 378, 383, 390, 584) on the inhibition by Pyribenzamine of the anaphylactic reaction in actively sensitized guinea pigs have appeared. Mayer (383) reported that 0.5–1.0 mg per kg of this drug was sufficient to prevent anaphylaxis Comparative studies (206, 462) showed that no wide variation in antianaphylactic activity existed between Antergan, Neo-Antergan, Benadryl and Pyribenzamine comparable to their effect on histamine shock. Protection of guinea pigs against immediate anaphylaxis was effected by exposure for three minutes to a 2 per cent solution of Pyribenzamine given by aerosol (387). Delayed anaphylaxis could be prevented in some animals by longer exposures, such as one of 10 minutes.

Antistine was found to be effective against anaphylaxis in actively sensitized guinea pigs (393, 507) and Hetramine protected against horse serum shock (190). Neohetramine was investigated by Reinhard and Scudi (437), who found it as effective as Pyribenzamine in protecting against anaphylactic shock in actively sensitized guinea pigs, but Bernstein and Feinberg (32) noted that it required 10–20 mg. per kg to give 70 per cent protection, whereas the Friedlaenders (207) showed that the same amount of protection was afforded by 3 mg per kg. Halpern (249, 250) reported on a series of compounds with a thiodiphenylamine nucleus, including 3015RP and 3277RP (Phenergan), and he found that 0.1 mg per. kg. of the latter was sufficient to protect guinea pigs against fatal anaphylactic

is often a froglike posture, with the hind legs extended behind the body (563). Death occurs only after 15–60 minutes, at times after many hours. The lungs show moderate emphysema and the intestine and stomach are congested and hemorrhagic.

PREVENTION OF ANAPHYLACTIC SHOCK

Since histamine is significantly involved in anaphylaxis, the antihistaminic drugs would be expected to be effective in diminishing the anaphylactic reactions in each species. Numerous reports have appeared which indicate that those antihistamines which effectively antagonize the bronchoconstrictive action of histamine are capable of diminishing the severity of anaphylaxis in the guinea pig, in which animal bronchoconstriction is the prominent feature of anaphylaxis. Thus, following the report (195) that certain phenolic ethers had the property of inhibiting or counteracting the action of histamine, Staub and Bovet (517) found that the compound designated as 929F (2-isopropyl-5-methylphenoxyethyldiethylamine), had definite antianaphylactic properties since it protected actively sensitized guinea pigs against a shocking dose of horse serum. Staub (514, 516) and others (465) confirmed this effect. Historically, the next drug studied was 1571F (N,N-diethyl-N'-phenyl-N'-ethyl-ethylenediamine) and it, too, was found to possess antihistaminic and antianaphylactic properties (247, 514, 516, 574).

Following these, there were described the antianaphylactic properties of Antergan (247, 344) and 2325RP (N'-phenyl-N'-ethyl-N-dimethylethylenedi-

amine (247). Bovet, Horclois and Walthert (49) discussed 2786RP or Neo-Antergan and established its value as an antianaphylactic agent. Many reports (18, 378, 383, 390, 584) on the inhibition by Pyribenzamine of the anaphylactic reaction in actively sensitized guinea pigs have appeared. Mayer (383) reported that 0.5–1.0 mg. per kg of this drug was sufficient to prevent anaphylaxis. Comparative studies (206, 462) showed that no wide variation in antianaphylactic activity existed between Antergan, Neo-Antergan, Benadryl and Pyribenzamine comparable to their effect on histamine shock. Protection of guinea pigs against immediate anaphylaxis was effected by exposure for three minutes to a 2 per cent solution of Pyribenzamine given by aerosol (387). Delayed anaphylaxis could be prevented in some animals by longer exposures, such as one of 10 minutes.

Antistine was found to be effective against anaphylaxis in actively sensitized guinea pigs (393, 507) and Hetramine protected against horse serum shock (190). Neohetramine was investigated by Reinhard and Scudi (437), who found it as effective as Pyribenzamine in protecting against anaphylactic shock in actively sensitized guinea pigs, but Bernstein and Feinberg (32) noted that it required 10–20 mg per kg. to give 70 per cent protection, whereas the Friedlaenders (207) showed that the same amount of protection was afforded by 3 mg per kg. Halpern (249, 250) reported on a series of compounds with a thiodiphenylamine nucleus, including 3015RP and 3277RP (Phenergan), and he found that 0.1 mg. per. kg. of the latter was sufficient to protect guinea pigs against fatal anaphylactic

shock. It was noted that Thephorin had greater efficiency in antagonizing histamine shock than active anaphylactic shock (330). Thenylene was found to alleviate active anaphylaxis in horse-serum–sensitive guinea pigs (468) and the same effect was reported for Diatrin (158). Treatment with 3 mg. per kg. chlorcyclizine prevented anaphylactic death when given one hour before the shocking dose (179). In a comparative study, Landau, Marriott and Gay (320) noted that larger doses of drug, about 3 mg., were required to protect guinea pigs against active anaphylactic death than were required for protection against histamine shock and that the various compounds tested (Antistine, Benadryl, bromothen, chlorothen, Histadyl, Pyribenzamine and Neo-Antergan) were almost equal in protective action, except for Antistine.

The rather extensive comparative evaluation by Feinberg, Malkiel, Bernstein and Hargis (187) included the effect of the antihistamines on active anaphylactic shock in the guinea pig Twenty-four drugs were tested for antianaphylactic activity Phenergan, 3015RP, Thenylene (Histadyl), Decapryn, 01780 (Lilly) and Perazil (Di-Paralene) were of about equal effectiveness, in that *3 mg. per kg. completely prevented shock. Benadryl,* Pyribenzamine, Neo-Antergan, C5581-H (Bristol), 01003 (Lilly), Thephorin and Trimeton were of the same potency, 3 mg per kg. protecting about seven out of 10 animals. Chlor-Trimeton was slightly more adequate. Decreasingly effective were Tagathen, bromothen, 194B (White) and 47-83 (Burroughs Wellcome) followed by Antistine, Hetramine, Neohetramine

and p-fluorobenzyl-DPE (Lederle). Orthoxine showed no protection in doses of 60 mg. per kg It should again be noted that these results are applicable only to this series and type of experiments and do not have to be comparable with those of other technics.

As has been previously observed, greater amounts of the antihistamines are required for protection against anaphylactic shock than for protection against histamine shock. The advantage of a comprehensive series of experiments, all conducted with the same technic, is that it enables comparisons to be made. In particular, it is more difficult to evaluate and compare antihistamines by the modification of the anaphylactic reaction, for, compared with histamine assays, it is more difficult to obtain a MLD_{50} or MLD_{100} for an antigen. Consequently, the shocking dose is usually an unknown multiple of the MLD, depending on the sensitivity of the test animal Thus, quantitation cannot be rigidly controlled and the drugs can only be compared for approximate relative potency However, a comprehensive series tends to minimize the variable factors which include mode of sensitization, length of incubation period, individual animal variation and the like. Evidence of these difficulties is found in the report by Campbell *et al.* (74) of the failure of Benadryl to protect actively sensitized guinea pigs against a challenging dose of the antigen, egg white, administered intraperitoneally. The authors used this evidence to indicate that a substance other than histamine is responsible for anaphylactic shock. Control animals were killed by the antigen.

The antihistamines likewise protect guinea pigs pas-

sively sensitized. Loew and Kaiser (350) investigated a series of benzhydryl alkamine ethers by this technic and found that Benadryl was highly effective. Friedlaender *et al.* (205) found no difference in the effectiveness of Benadryl and Pyribenzamine. Neohetramine, however, was less effective; with doses of 5 mg. per kg. survival was only 60 per cent, compared with 100 per cent survival when Pyribenzamine was given in doses of 1 mg. per kg. (486). Decapryn (61) and AH289 (chlorcyclizine) (470) also altered anaphylactic shock in passively sensitized guinea pigs. Pyribenzamine and Neohetramine were found to have but little protective action in reversed anaphylaxis in the guinea pig in which the shocking antigen was rabbit serum immunized to guinea pig serum (19). The nature of this shock makes it acutely fatal, but the authors stated that some degree of protection could be attained with "weaker" serums

Antihistamines show varying results in modifying the anaphylactic response in animals other than guinea pigs. Halpern (247) indicated that Antergan, 1571F and 2325RP prevented fatal anaphylactic shock in sensitized dogs. Pyribenzamine (383) and Benadryl (570) were also effective. Mayer and Brousseau (386) reported that 25 mg. per kg of Pyribenzamine decreased the mortality rate of actively sensitized mice from 89 per cent for the unprotected to 42 per cent for the protected. On the other hand, Decapryn (61) in amounts as high as 175 mg. per kg. had no effect on active anaphylaxis. Antihistaminic drugs had but little effect on shock reactions of actively sensitized fish (141).

The antianaphylactic activity of the antihistamines

has also been demonstrated by in vitro experiments. Thus, Halpern (247) demonstrated that Antergan, 1571F and 2325RP would prevent contraction of the sensitized guinea pig ileum by the specific antigen. In addition, Wilcox and Seegal (574) noted that in a perfused sensitized guinea pig heart, 1571F prevented the diminution in coronary flow caused by the antigen. Increased heart rate and amplitude were not prevented. The authors emphasized that the large amounts required (5 mg per liter) to modify the anaphylactic reaction in the perfused heart "indicates that other factors must also play a part in anaphylactic shock." Benadryl, Neo-Antergan, Pyribenzamine and Antergan were about equal in their inhibiting effect on the isolated, sensitized guinea pig ileal strip (462). Thephorin also performed the same function (109). However, the constriction of the bronchioles by the antigen in a perfused, sensitized lung preparation could not be prevented by Pyribenzamine (584).

Even though the antihistamines show such a profound influence on the manifestations of the antibody-antigen reaction per se, they are without immunologic effect in that they do not modify antibody production (344), precipitin or complement titer (18) or immunization activities in general (388).

Influence on Other Immunologic Responses

Closely related to the systemic anaphylactic reaction is the Arthus reaction. This is an anaphylactic reaction, although local in site, the severity of which is directly proportional to the amount of precipitin available at the

site of contact with the antigen, and is the result of antibody-antigen union. The tissue damage, usually consisting of a large, edematous, hemorrhagic and necrotic area, is the direct result of vascular damage, necrosis of the capillaries and terminal arterioles, interstitial edema and hemorrhagic and cellular infiltration. The damage to surrounding tissue appears to be due to the interference with nutrition which results from the vascular damage and from the clogging of the tissue spaces with hemorrhage and exudate. In light of the relationship of the Arthus reaction to hypersensitivity it is understandable why the effect of antihistamines on the reaction was investigated However, in contrast to their effect in typical anaphylactic reactions, the antihistamines were found without influence on the course of this localized hypersensitivity reaction (119, 140, 194, 323), a result which seems to indicate that histamine plays no role in this phenomenon

There is much evidence that the antihistamines do not affect the bacterial or tuberculin type of sensitivity reactions. Early in the history of these drugs Boquet (42) noted that 883F, 929F and Antergan failed to alter the tuberculin reaction in guinea pigs; he used chiefly 1:10 OT. The results with Antergan were later corroborated by Kreis (312). Fischel (194) confirmed these observations in his experiments on rabbits. Using both a purified protein derivative of tuberculin and a nucleoprotein fraction from a hemolytic streptococcus, he noted that the bacterial type of reaction was not altered by Pyribenzamine administered orally before and during the day of testing. Pyribenzamine also failed to

protect against the systemic tuberculin shock in the tuberculous guinea pig (562), and Neohetramine did not affect the reaction from 1 mg OT (142). According to Sarber (478), some of the negative results were obtained because the doses of tuberculin used were too large and only one dose of the antihistamine was given. Using threshold doses of OT and giving the infected guinea pigs 25 mg per kg of Benadryl subcutaneously twice daily before and during the reaction period, he concluded that there was a definite trend toward lessening of the reactions

By experiments on induced sensitization and allergic dermatitis, Mayer (384) proposed additional evidence that histamine plays an active role in the development not only of the initial phase of skin irritation but also of the contact dermatitis itself. He (385) reported on the effect of the antihistamines Pyribenzamine and Antergan on the inhibition of the inflammation of the eczematous reaction caused by sensitization to p-phenylenediamine Both drugs had a greater effect when applied *locally* as an ointment or in oil than when administered subcutaneously Brown and Werner (61) indicated that Decapryn given orally in large repeated doses or applied as an ointment also diminished the severity of lesions in guinea pigs sensitized to 2,4-dinitrochlorobenzene and p-nitrosodimethylaniline

The evidence regarding the effect of the antihistamines on production of experimental hypersensitive vascular and cardiac lesions, such as periarteritis nodosa and myocarditis, is controversial. The technics used to produce these conditions simulate those of Rich and

Gregory (444) in that sterile horse serum is injected into rabbits intravenously with or without a subsequent dose. Kyser and associates (315, 316), investigating Benadryl and Searle antihistaminic drugs No. 1694 and 1627, noted that complete protection was afforded to all sensitized animals who had the concomitant use of the drug during the sensitization period. On the other hand, Roberts, Crockett and Laipply (448) and MacGregor and Wood (368) failed to confirm this observation with Benadryl. Roberts *et al.* used Benadryl in doses of 5 mg. per kg. twice during the course of the experimental procedure, just before the second and third sensitizing doses MacGregor and Wood, however, did use larger amounts of Benadryl, giving up to 10 mg. per kg twice daily for the 20 days during which the experiment was in progress. In neither report was any difference noted in the myocardial and endarteritic lesions which followed sensitization The lesions were essentially those described by Rich and Gregory (444)· there was a patchy or generalized arteritis with medial necrosis, a periarterial reaction in the adventitia with polymorphonuclear and eosinophilic leukocytic infiltration, small nodule formation, occasional valvular and endocardial lesions, and edema and necrotic collagen tissue near the severely affected vessels. These dissenting results indicate the need for additional experimentation before concluding what the value of the antihistamine is to be in experimental serum-induced myocarditis and other manifestations. Related to this problem is the edema produced in the rat by the intraperitoneal injection of egg white. Rats have a natural hypersensitivity to this pro-

tein, Léger and Masson (329) observed that Antistine, Benadryl and Neo-Antergan were all effective in inhibiting this edema. They did not claim, however, that these results inferred that the edema was due to local histamine release. Brown and Werner (61) obtained the same results with Decapryn.

The antihistaminic drugs have been evaluated with regard to other incidental experimental conditions which may also be classed as allergic. Leopold, Dean and Blazar (333) observed that Pyribenzamine prevented the production of anaphylactic uveitis in rabbits when given systemically before the challenging dose. Administration of the drug at the same time as the shocking dose had no effect. Pyribenzamine did not inhibit production of typical experimental meningoencephalomyelitis in guinea pigs which were injected subcutaneously with emulsions of fresh guinea pig brain and Freund's adjuvant (9) The animals had received, over the course of the experiment, weekly subcutaneous implantations of 500 mg Pyribenzamine pellets in beeswax. Reubi (440) reported that Ciba's experimental antihistamine No 5512M prevented the nephritis produced in rabbits by antiserum injections.

Bioassay in Man

THE MAJOR PURPOSE of assay of the antihistaminic drugs in laboratory animals is to obtain information on their potential therapeutic worth in man. In a general way animal assays accomplish this purpose. Drugs which have antihistaminic activity in animals by the same token possess antiallergic action in man. When one attempts, however, to translate quantitatively potency in animal work into clinical therapy one encounters a number of discrepancies and difficulties. In many of the early and some recent publications of experimental work on antihistamines, claims for potency were based on the number of lethal doses of histamine which can be inhibited in the guinea pig by large doses of the compound. On that basis, for example, Neo-Antergan was found to be four times as potent as Pyribenzamine and 25 times as potent as Benadryl. It is obvious from clinical experience that such figures have no bearing on clinical potency.

One of the possible explanations for this discrepancy is that the amounts of histamine concerned in clinical

allergy in no way approximate the enormous quantities used in animal experiments, and it may be possible that with small doses of histamine the antihistamines display no such wide ranges of potency. Other methods of histamine assay have indeed pointed to this idea as at least one explanation. On the basis of antagonism of only one lethal dose of histamine it has been found that these drugs show more moderate differences in activity. A number of experimental technics in the laboratory, such as the inhibition of one lethal dose of histamine, the inhibition of bronchospasm from histamine aerosol and the prevention of histamine contraction of the ileal strip, have shown some quantitative relationship to one another and to antiallergic effect. The relationship to antiallergic effectiveness has not been quantitative in the strict sense of the word. Nevertheless, a drug which assays as very weak by such methods is not potent for man, whereas another which has potent antihistaminic action also turns out to be potent in its antiallergic action.

In addition to the possible species differences in response between the laboratory animal and man, we cannot ignore the fact that in assaying antihistaminic action we may be overlooking responses other than that of histamine in the hypersensitive state. That such may be the case is particularly suspected from two observations. Inhibition of anaphylactic death in the laboratory animal is more difficult and requires a larger dose of antihistaminic drug than prevention of histamine shock. Clinical therapy is quantitatively closer in agreement with anaphylaxis than with histamine effect (219). Moreover, it should be pointed out that toxicity is measured in ani-

mals on the basis of convulsions and death, whereas in man it is measured in large part on the basis of sedation from moderate doses.

Therapeutic Evaluation

In the ultimate analysis, the value of a drug is judged by the capabilities it has to remedy the abnormal manifestations for which it is intended. When the manifestations are chiefly objective and constant this problem is relatively simple. Allergy, however, is characterized by a preponderance of subjective manifestations, varying in degree in different persons and at different times and with place, season, age, mental attitude and interpretation of the observer. To evaluate a remedy here, the problem becomes more difficult and the interpretation less secure. It is for this reason that the clinical literature on antihistamines is rampant with claims and conclusions which are misleading. It behooves the practicing physician to scrutinize each report on clinical therapy critically and to ask himself the question: "Has the observer considered these variables in his clinical investigation?" A brief discussion of the major variables encountered in the evaluation of antihistamines may be of help.

The patient.—A number of variables which concern the allergic patient must be considered in the interpretation of a therapeutic test. Age is a factor; children usually respond better than adults to antihistamines. The predominant symptom and the effect of the drug on a particular symptom of a syndrome is of significance. For example, the antihistamines are more effective against sneezing than against nasal blocking. Evaluation of the

effects of these drugs from this standpoint, as has been done by Sheldon and his co-workers (499), is rare. It is quite different, for example, to judge the potency of a drug on the basis of cases of mild urticaria and compare this potency with the effect another drug has in severe penicillin or sulfonamide reactions, which as a rule require several times the ordinary dose for effective results.

Allergic syndromes are prone to cyclic changes. The hay fever patient who has an hour of suffering in the morning cannot be tabulated as a therapeutic success if his symptoms cease 30-60 minutes after taking a pill. And if symptoms regularly last several hours in the morning, the duration of effect of the pill cannot be listed as 24 hours because he has no recurrence until the following morning (179). In many other allergic manifestations periodic fluctuation is the rule and a clinical effect should only be ascertained by repeated and consistent behavior

In assaying an antihistamine in hay fever it may be pertinent to know whether the group studied is average in intensity of symptoms or is a selective group. If mildness of hay fever is such that the patients seldom seek desensitization treatment, a large percentage will obtain benefit from antihistamines On the other hand, the allergist who sees the difficult cases which have been unresponsive to other measures is apt to find a lower incidence of effect from these drugs. Everything else being equal, it has been found that those patients who take desensitization treatment respond better to the drugs than do those who have had no desensitization therapy (16, 178, 212, 564)

The mental attitude of the patient is not to be ignored. We know some patients who claim improvement from every type of antihistamine, no matter what the dose, and even from a placebo tablet. Others will admit no improvement even when objectively one can see that it is present. It matters, therefore, what type of group is being evaluated, whether it is a clinic or private group, a laboring or professional group, a phlegmatic or more emotional class

Environmental variables.—In seasonal hay fever especially, the environmental variables are tremendous. Grass hay fever as a rule responds much better to antihistamines than does ragweed, primarily because the seasons are usually less severe. One cannot compare on an equal basis the results of antihistamine therapy in ragweed or mold cases in New York City, Chicago and Los Angeles, where the quantitative pollen differs materially. A drug studied in a mild hay fever season cannot be justly compared with another drug tried in a severe season. Drugs cannot even be compared during the same season if one drug is used one part of the season and another drug the next; for example, the later stages of hay fever due to nasal stuffiness are less likely to be influenced than are the earlier symptoms of sneezing and rhinorrhea. It is regrettable that in most reports on clinical evaluation these factors are ignored or, if mentioned, are often dismissed with the inference that they are outweighed by the findings (288).

Other conditions.—Comparison of results by different observers, with different seasons, different drugs and different locales, is almost worthless. This has been empha-

sized by Loveless and Dworin (360) in their review. Even if the results are combined or averaged their significance is questionable. Indeed, too many of the reports have virtually no basis for comparison, other than perhaps the difference between using and not using an antihistamine One of the most critical means of evaluation is the use of the crossover trials in which one drug is compared with another intermittently (15, 178, 201, 359). Another method is to employ a separate group of subjects for each drug during the same period. It is risky even for the same observer to compare one drug in one season with another in the next unless due care is observed in equalizing the conditions

The criteria for effects are often ignored and usually not even mentioned. While it is futile to count the number of sneezes, some rough criteria of symptoms, such as the number of hours of discomfort, days of disability, etc, can be made Placebo controls are often advisable (564) although they are not necessary if an array of antihistamines of varying potency is used. Observers who do only an occasional therapeutic trial of this sort are urged to make a control study with placebos, preferably in the same patients receiving the antihistamines.

The number of patients observed must be adequate. How many patients are actually needed to make results in the group significant depends on a number of factors, including the experience of the observers, the methods of observation, the frequency with which patients are seen and the purpose of the observations. Thirty patients with hay fever, for example, would be sufficient to note whether a drug is effective, but it might take 10 times

that number to serve as a basis for comparison with another drug.

The difficulties of assessing toxic effects are perhaps even greater than those in evaluation of therapeutic results. The very severe toxicities offer no difficulties, but the more moderate may be largely dependent on the type of patient, the attitude of the observer, and the dosage used.

It should be mentioned that some conditions, particularly dermatoses (308), lend themselves better to objective analysis. Perhaps other conditions also could be studied more objectively, such as asthma by respiratory function tests or allergic rhinitis by nasal air flow.

The clinical investigator.—When objective findings are of least help the reliability of the observer becomes paramount. A clinical therapy report in which the investigator is biased, selfish, lacking in integrity or without critical observation can and does mislead. Those who have sufficient experience in the field learn to judge the report for what it is worth. Some clinicians are inclined to grow increasingly enthusiastic with each new antihistamine; others may display insufficient clinical awareness, while still others actually lack the experience necessary to enable them to evaluate the drugs properly. It is even possible for an observer's attitude to change honestly with advancing developments. For example, it is fair to say that with the acceptance of the value of the antihistamines we have now set for ourselves more rigid criteria for effectiveness than we did several years ago. The net result is that whereas four or five years ago a given drug was recorded by us as being effective in 80

per cent of hay fever patients, perhaps now with our modified standards this incidence might be only 65 or 60 per cent.

Objective Methods

It is thus apparent that the experimental laboratory cannot give the direct answer to the therapeutic value and potency of an antihistamine and that a clinical therapeutic evaluation is long drawn out, requires many subjects and has many pitfalls Objective methods which could be applied to man would offer many advantages. Such objective procedures attempt mainly to assay quantitative inhibition of histamines, the local antigen-antibody whealing and the toxic effects of the drug.

Histamine asthma—Bronchoconstriction in man has been produced by Curry (112) who found that it could be inhibited by the administration of an antihistamine. This technic could probably be quantitated to study antihistaminic activity of a drug. However, human bronchoconstriction produced by an aerosolized allergen is apparently not readily prevented by the same drugs. In line with these experiments, it has been found (341) that in asthma spirometric changes following administration of Benadryl were negligible, whereas after epinephrine or aminophylline the changes were decided.

Histamine wheal and flare.—The capacity of human skin to respond to histamine by wheal and flare has been known for a long time. This responsiveness and its normal variations have been studied quantitatively with the histamine introduced by electrophoresis (500), intradermally and by abrasion technic (358). We have

shown that the flare as well as the wheal response is in proportion to the concentration of the histamine applied and that the flare size can be more easily measured. In 1942, Parrot (415) demonstrated that the histamine wheal and flare could be inhibited by Antergan. Friedlaender and Feinberg (204) several years ago reported a study in which the wheals of histamine, antigen-antibody reactions and other whealing agents were inhibited by local and oral administration of Benadryl.

Rough quantitative studies on electrophoretic introduction of histamine and Pyribenzamine were reported in 1947 by Aaron and Abramson (2). Schwartz and Wolf (484) compared the potency of antihistaminic drugs by noting the incidence of inhibition of wheals and flares from histamine 1:1,000 and ragweed 1:40 when 5 per cent (or 2.5 per cent) of the antihistamine was applied on the scratch Such a technic could by no means be regarded as quantitative, and it led to such obviously incorrect interpretations that Antistine had greater antihistaminic activity than Pyribenzamine and greater antiallergic effect than Benadryl. Bain (24) made an impressive quantitative study by using intradermal injections of graded doses of histamine and antihistamine.

We felt that perhaps quantitative inhibition of the histamine wheal and flare on the human skin by local application of the antihistamine might be useful in the assay of these drugs. Such an assay, if reliable, could be done on a few subjects and would not require long periods of clinical observations. Although not to be regarded as the final evaluation, it could, nevertheless,

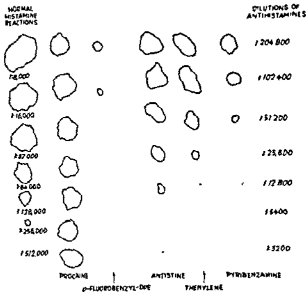


FIG. 2.—Quantitative inhibition of histamine reaction. Sensitivity of subject is determined by titration of histamine dilutions applied to series of scratches on the back. Dilutions of antihistamines are placed on several abraded areas at the same visit. After 10 minutes the drugs are washed off, and a drop of the concentration of histamine which gave one-half maximal flare (1:64,000 in this case) is applied to each site. Flares occurring about 10 minutes later are outlined with a ballpoint pen and the tracings transferred to paper. The different degrees of inhibition with various drugs are noted in the figure above. This assay is repeated on 20–40 subjects and the results averaged.

serve as a screening program to indicate which drugs are worthy of clinical trial. After several years of investigation we (358) adopted the following technic which we used for the evaluation of a large series of drugs.

Histamine reactions are titrated on normal subjects using histamine solutions from 1:8,000 to 1:512,000 (in terms of base), in increments of 100 per cent, placed on circular abrasions made by a piece of hollow

TABLE 1.—INHIBITION OF HISTAMINE FLARE BY TOPICAL APPLICATION OF ANTIHISTAMINE

	Relative Potency %		Relative Potency %
Pyribenzamine	100	Pyrrolazote	53
Benadryl	38	Decapryn	75
Neo-Antergan	60	C5581-H (Bristol)	31
Antistine	28	Thephorin	28
Thenylene	53	*Trimeton*	35
Phenergan	40	01780 (Lilly)	14
3015 (Rhone-Poulenc)	21	01003 (Lilly)	12
Chlorothen	48	194B (White)	53
Neohetramine	25	p-Fluorobenzyl-DPE (*Lederle*)	*200*

tubing about 1 mm. in diameter After the flares are traced, the histamine solution giving one-half maximal flare is used in the inhibition test. The antihistaminic drug is placed on a series of abrasions in dilutions of 1:204,800 to 1:3,200, and after 10 minutes the drops are washed off and the histamine applied Reactions are noted in about 10 minutes. Usually three or four drugs are thus compared at the same time on the subject's back. *A number of subjects are used for each experi*ment. The difference between the end point of different drugs is regarded as a measurement of difference in inhibiting power.

As a whole this method has shown good clinical

agreement for all but one or two compounds. It is recognized that at best this technic can only measure the effect on histamine. Similar evaluations of the allergic reaction might be more dependable. Furthermore, this method does not take into account variations in absorption, time lag and other metabolic effects which might be factors in administering the drug orally. The mediocre results on local application of Phenergan and chlorcyclizine might well be explained on some such basis

In the past two years we (75) had been working on a method by which such histamine and antigen reaction can be studied after ingestion of antihistamines. There are a number of difficulties with this technic, primarily because large doses of drug are required to produce any effect which can be quantitated Meanwhile a number of other workers have reported procedures based on similar principles

Kallos and his associates (294) reported in 1947 that the intensity of the histamine flare and its inhibition by Antistine could be measured and thus quantitated. Bain and co-workers (24, 25) found that after oral administration of antihistamine the log-dose–response curve to intradermal histamine shifts to occupy at any given time a new position so that there is an equal percentage reduction of wheal area of the test doses of histamine over a range of 0.03–10 μg. If this dose-response curve is determined on several subjects and repeated with other drugs, since the dose-response curves are parallel, the mean relative weight-for-weight potencies can be estimated On this basis they found that

Phenergan was 15 times more potent than Antistine and seven times more potent than Neo-Antergan. The duration of one-half maximal effect on the wheal for Phenergan was 5.6 times greater than that for Antistine and 3.8 times greater than that for Neo-Antergan. Careful clinical observations of the effect of Phenergan and Neo-Antergan on chronic urticaria agreed well with the antiwhealing assays. Benadryl was found to be rather weak and had short-lasting effect.

Jaros and his associates (289) compared chlorcyclizine with Pyribenzamine by noting the effect of the oral administration of these compounds on the histamine wheal inhibition. Since wheals as small as 0.5 mm. were recorded, the dependability of interpretations from such a study are open to question Serafini (493) also showed the varying degrees of inhibition of wheals and flares from different concentrations of histamine after oral administration of an antihistamine However, he did not develop the method to employ it for potency studies

The effect of various antihistamines given orally on the skin histamine reaction threshold by iontophoresis was studied by Perry and his associates (423). In order of decreasing effectiveness, the drugs tested ranged as follows: Hydryllin, Pyribenzamine, Benadryl, ephedrine and aminophylline. Sternberg and co-workers (521) used a similar technic From their results they concluded that Pyribenzamine, Benadryl, Neo-Antergan and Hydryllin were the most potent and about equally effective. From there on, in diminishing effectiveness were listed Thephorin, Diatrin, Trimeton, Decapryn, Tagathen, Thenylene and Histadyl, Neohetramine and Antistine.

The authors inferred that these findings correlate closely with clinical experience. Not only do some of these findings disagree with ours, Bain's and those of other experimenters, but they also are not in accord with many of the clinical observations. Furthermore, there are obvious discrepancies in the data and graphs. Thenylene, 100 mg., is listed as being identical in potency with Histadyl, 50 mg.; both are trade names for the same drug, methapyrilene. The wide fluctuation of responses in individuals, the use of only 10 subjects for each evaluation and the use of different subjects for each drug introduce so many variables as to make the interpretation doubtful.

Peck and his associates (417) studied the effect of various routes of administration of Pyribenzamine on the wheal produced by 0.05 cc. of 1:10,000 histamine phosphate given intradermally. They found that oral administration, local injection and iontophoresis reduced the histamine wheal and flare, while ointment had little effect on the histamine reaction. On the other hand, in epidermal sensitivity, where the skin was broken, Pyribenzamine was absorbed from the ointment, since good therapeutic results were obtained. Nilzen (407) showed that a mixture of antihistamine with histamine reduced the wheals caused by the latter when applied by scratch or intradermally. In order of diminishing effectiveness the antihistamines ranked in the following order: Neo-Antergan, Antergan, Thenylene, Benadryl, Pyribenzamine, Antistine, Neohetramine, and Thephorin.

Inhibition of allergic wheal.—Vallery-Radot and coworkers (551) made quantitative studies on the inhibition of local passive transfer reaction. They determined

the dose of drug necessary to completely inhibit the reaction. It was found that the dose of Phenergan was only about 30 per cent of the dose of Neo-Antergan or Antergan. The duration of action of Phenergan was much longer. The doses required for the inhibition of this wheal were greater than those required for therapeutic effects. The effects on direct skin tests have also been observed. More work on this phase of assay is in progress in our laboratory.

Toxicity assay.—Mention has already been made of the evaluation of the toxicity index of an antihistamine. Such evaluations have the same inherent difficulties as therapeutic trials, with perhaps the additional disadvantage that objective signs are usually absent. Objective tests would offer a more critical basis for assay of toxicity. Holtkamp and his associates (273) reported an objective assay. By using tests of mental ability, reaction time, two-point discrimination distance and other technics they measured the effects of therapeutic doses of Benadryl, Pyribenzamine and Hydryllin. With these drugs there is an appreciable change in all the mental tests in over half the subjects. Pyribenzamine affected the greater number, but Benadryl occasionally produced effects of considerably greater magnitude. Hydryllin caused increased efficiency in most subjects but decreased it in a few.

CHAPTER 6

Respiratory Allergy

THE MAJOR syndromes of allergy of the respiratory tract are seasonal hay fever, nonseasonal vasomotor rhinitis, persistent or recurring cough (particularly in children) and asthma. The antihistaminic drugs do not affect all of these manifestations to the same degree. the differences will be pointed out in the ensuing discussion. Furthermore, since this manual concerns the antihistamines one might gain the impression that these drugs are extolled as the main or only treatment of respiratory allergy It is therefore important at the very beginning of the description of antihistamine therapy to call attention to the fact that other forms of therapy are not only helpful in addition to antihistamine therapy but may be the only effective remedies in some patients or under certain conditions.

ANTIHISTAMINES IN HAY FEVER AND PERENNIAL VASOMOTOR RHINITIS

Of the allergic respiratory manifestations, seasonal hay fever has responded best to the antihistamines. In

perennial vasomotor rhinitis, whether due to allergic factors or so-called "intrinsic," results have not been as good. This difference is more likely due to differences in the secondary changes produced by long-lasting nasal allergy than to differences in the nature of the allergen. The effects of antihistamines on the nasal symptoms are purely palliative and in no way shorten the duration of the entire syndrome, except as the prevention of severe congestion may to a certain extent prevent the production of secondary tissue changes. Each dose of drug is effective for only a few hours at a time. From experimental and clinical studies it can be assumed that these drugs have no influence on the immune response in allergy, that is, they neither interfere with the production of immune bodies by desensitizing injections nor do they increase the immune substances.

Effect on symptoms.—The hyperesthetic manifestations of nasal allergy, such as tickling of the nose, sneezing and itching of the eyes and palate, are the symptoms most susceptible to palliation with antihistamines (499). The rhinorrhea is usually also modified, although with large doses or in some persons with small doses the drying effects on the nose and throat may be so pronounced as to become objectionable features of such therapy. Indeed, it is this drying effect occurring in some persons which is the major basis for the belief, encouraged by some, that these drugs are effective remedies for the infectious cold. The nasal obstruction is also benefited, but usually to a less extent and in fewer patients than is the case with the other symptoms (174, 175, 178). It is thus easy to understand why the later stages of hay

fever are not so frequently or effectively benefited by the antihistamines. It is also not surprising that the types of hay fever which have long seasons and chronic vasomotor rhinitis show less response to these drugs. Whether this difference in response signifies the presence in those boggy turbinates of a mediator or mechanism in addition to histamine or merely the presence of a larger amount of histamine has not been settled. The fact that topical application of an antihistaminic drug in such difficult cases has often been helpful lends credence to the histamine-excess hypothesis.

It cannot be overemphasized that the asthma associated with hay fever is not prevented appreciably by the antihistamines. Hence, no matter how effectively the nasal symptoms may be controlled by these drugs, those persons who have had (or are destined to have) an associated asthma will, as a rule, continue to have it. Since desensitization therapy effectively prevents asthma in patients with pollen or mold allergy, it is unjustifiable to substitute the antihistamines for such therapy in these patients. Since about 35 per cent of the patients with ragweed hay fever have an associated asthma and since the asthma may be initiated in the early or later years of the sufferer's hay fever, it follows that any person who depends on the antihistamines for relief may be confronted at any season with asthma.

Occasionally a dose of an antihistamine given about one hour before a desensitizing injection may be useful in preventing local and systemic reactions in highly susceptible persons. When the desensitizing dose cannot be appreciably increased because of repeated constitutional

reactions, moderate increments may be made with the aid of the antihistamine; however, it is rarely possible to give very large doses, such as several tolerance doses, in this manner. Antihistaminic drugs should not be used routinely for this purpose.

Almost from the beginning of our clinical experience with antihistaminic drugs in 1945 we learned to utilize them as diagnostic agents in differentiating questionable nasal allergy from colds or chronic nasal infections Thus, we administered an antihistamine to patients with known allergic rhinitis when the question arose whether the current episode was a recurrence of the allergy or an infectious cold, and to patients with chronic nasal symptoms which could not be identified definitely as infectious or allergic. When the symptoms were well controlled by repeated doses of the drug, subsequent developments showed that we were dealing with an allergy. If the symptoms were not definitely controlled, developments indicated that many of them were of an infectious nature.

Dosage and administration.—Although this subject will be discussed in detail in Chapter 9, some of the salient points of the methods of use of antihistamines in nasal allergy may be briefly mentioned. It has been the custom of many physicians to prescribe these drugs several times daily at regular intervals for hay fever and perennial rhinitis. Such dosage should only be required in patients who have continuous symptoms, and they are in the minority. Most patients will require only a morning dose, with perhaps an additional evening or bedtime dose. When the symptoms occur irregularly, it may be

well to instruct the patient to take the drug as needed. In some instances the use of a bedtime dose may relieve the nasal congestion so that the morning symptoms are lessened. At times this effect may be achieved more adequately by longer acting or enteric-coated antihistamines. For most of the drugs the effect lasts not longer than about four to six hours (334). More lasting effects can be obtained in a large percentage of patients with Phenergan or chlorcyclizine (Di-Paralene or Perazil).

The average dose of most drugs for nasal allergies is 50 mg. To achieve the same effect with drugs such as Neohetramine and Antistine a dose of 100 mg. or more is required. On the other hand, Decapryn in 25 mg. doses is quite effective, whereas in 50 mg. doses it is too sedative for most persons. The average dose of Phenergan is 15–25 mg. Chlor-Trimeton is customarily used in 4 mg. doses, although many patients require doses of 8 or 12 mg. Toxicity with the latter doses is apt to be severe. Children are given smaller doses. Although it is characteristic of these drugs that children often tolerate them in amounts as large as those given adults and frequently tolerate them better, this applies only to moderate doses, when sedation is the major toxic effect. Children are more prone to excitatory effects from the antihistamines, behaving in this respect like the laboratory animal. From the records of toxic effects in children and of the fatal results it is suspected that in excessive dosage these drugs may be more dangerous to children.

In patients with nasal allergy resistant to oral medication, topical application may be helpful. We have found that solutions in the form of nose drops are frequently

irritating, whereas a fine spray, particularly the mist type obtained with a nebulizer, is better tolerated. The spraying may have to be repeated a number of times at frequent intervals before evident results are obtained.

Incidence and degree of effect.—With full therapeutic doses our experience indicates that 50–80 per cent of seasonal hay fever patients in the Midwest will obtain sufficient benefit to make use of these drugs worth while. The incidence of relief in perennial vasomotor rhinitis will be about 40–65 per cent. The variation in these percentages is primarily due to the different effects of different drugs but is also caused by seasonal differences Spain and Pflum (511) reported the results obtained by collaborators with the Committee on Therapy of the American Academy of Allergy. Benadryl, Pyribenzamine, Neo-Antergan, Hydryllin and Trimeton were used In 60–75 per cent of patients with seasonal hay fever there were varying degrees of improvement, while in nonseasonal rhinitis 50 per cent benefited.

In the evaluation of any report, it should be realized that the standards of observers differ. Some practitioners may classify occasional benefit from the drug as a positive result. Others regard any deviation from the usual symptoms, no matter how slight, as an instance of improvement. Others may be so conservative as to demand benefit every time the drug is used in a particular person. It is difficult, of course, to set precise standards in a condition which is mainly subjective in nature. The best criterion of effectiveness we have been able to employ is the ability of the drug to be productive of results worth while to the patient in the majority of episodes

of his disease. We have been skeptical of any results classified by ourselves or others as "fair."

A number of factors determine the likelihood of a beneficial result in any individual or the incidence of benefit in a group. The most puzzling of these is an individual variation which does not appear to be dependent on the severity of the allergy. Some persons fail to respond to any antihistamine despite the fact that they have mild symptoms Others are benefited by one drug and not by another, although the latter may be more potent for the majority. This individuality is not only of practical importance in therapy, but the solution of its mechanism would probably shed much light on the antigen-antibody or histamine mechanism.

In general, the severity of the nasal symptoms will determine the likelihood and degree of benefit. Thus, patients with mild hay fever or sporadic and mild perennial allergy may do exceedingly well with antihistamine therapy Patients with the milder varieties of hay fever, such as tree pollinosis, and many grass-pollen-sensitive patients may also obtain good results, whereas a larger proportion of ragweed cases may be resistant to the drugs By the same token, the results can differ substantially in different parts of the country The Bostonian who has ragweed hay fever has a better opportunity to be benefited by an antihistamine or by a moderate amount of desensitizing treatment than the Chicagoan with the same disease. And, as a corollary, it is not surprising that the incidence of results observed or the amount of drug required to achieve results may differ for the Boston and Chicago physician

Even the season in any locality may differ from year to year and influence the results. Thus, in reporting the results of antihistamine therapy during the 1946 ragweed season we (174) made the cautionary statement that results in more severe seasons may not prove to be as good. This has actually turned out to be the case. *Since all drugs are not evaluated in any one season*, it is important to know, if possible, during which season the observations were made and to take the severity of the season into consideration.

In the early part of the season the hay fever sufferer may respond well to antihistamines. When the pollen or mold spore content of the air becomes high as the season advances, the effectiveness of therapy may decrease or the therapy may be completely inadequate. In the later part of the season, even when the amount of pollen or mold spores is diminishing, the stage of nasal stuffiness may be more pronounced. Then the chances for effective results are not as good as they are in the stage of sneezing and rhinorrhea.

Desensitization therapy, whether in pollen, mold or dust allergy, if it does not abolish a large part of the symptoms, is at least likely to turn a severe allergy into a milder one. Hence, it is not surprising to find that the antihistamines are more effective in desensitized than in *nondesensitized patients.* Even when no apparent clinical result can be observed from desensitization, antihistamine therapy is apt to be more effective (16, 41, 178, 212, 564). Blumenthal (41) obtained relief of symptoms in about 56 per cent of patients with desensitization

alone, in 47 per cent with antihistamines alone, and in 88 per cent with combined therapies.

Patients frequently remark that a dose of an antihistaminic drug which previously helped them is no longer as effective If all the seasonal factors and variables previously discussed are eliminated and if only the stabilized forms of chronic rhinitis are considered, there would appear two alternative explanations. One is that the sufferer, after some period of partial relief which was originally appreciated and properly classified, has now unconsciously set for himself a new standard. Since he still has symptoms which he would like to dispose of, he now feels that the antihistamine is not doing much for him. Native Bostonians or New Yorkers complain as much from ragweed hay fever as do those who live in Chicago or Indianapolis. Each has created a standard and he knows no other, unless perchance he visits the other locality Thus it may be with different levels of symptoms before and after continued antihistamine therapy. On the other hand, it is not inconceivable that a tolerance for the drug may actually develop A tolerance for the sedative action appears to be common after continued use of an antihistamine. At any rate, the question is important practically and theoretically and we are now engaged in a study of this problem. Our preliminary results (119a) indicate that continued administration of an antihistamine produces a diminished ability of the drug and related drugs to inhibit the skin reaction to histamine and to antigens. The findings of Monash (397a) are similar.

ANTIHISTAMINES IN ASTHMA AND ALLERGIC COUGH

A spasmodic and recurring cough, without wheezing and especially without dyspnea, is a frequent allergic phenomenon in children and may also occur in adults. It is usually associated with nasal allergy, although at times the latter may be absent. Such coughs often respond favorably to antihistaminic drugs. For example, of nine such patients in one series, Thenylene was found to be effective in six (182). The cough in the preasthmatic stage at the beginning of an acute attack of asthma may also be materially influenced by antihistamines.

Frank asthma, on the other hand, has in our experience proved to be virtually unresponsive to the antihistamines. We do not mean to imply that these drugs are of no help at all, but we emphatically maintain that seldom are they as effective or as useful as other remedies, such as ephedrine, epinephrine, Isuprel (Norisodrine), aminophylline and iodides. As an adjunct to other medications they may at times be of some aid. There are times when it is suspected that antihistamines may aggravate the asthma, possibly because of their drying effect on the bronchial secretions.

The majority of asthma specialists agree that the results with antihistamines in asthma are not as good as those in nasal allergy. Results of different observers range from a negligible incidence to about 70 per cent. No doubt much of this variation depends on the vicissitudes of the asthmatic syndrome. Many of the good re-

ports are probably due to continued antihistamine administration, when it is difficult to assign the result to the therapy Perhaps also some of the alleged relief from asthma is due to the general quieting effect of the sedative action of these drugs. In this connection an objective study made by Levy and Seabury (341) appears significant. Benadryl was given in 100 mg. doses to a series of asthmatic patients; for a comparison of effect, some were given 0.3 mg. epinephrine subcutaneously or 0.25 Gm. aminophylline intravenously. One-half and one hour after Benadryl administration determinations of the vital capacity, tidal air, minute ventilation, expiratory differential, respiratory rate and degree of emphysema showed no consistent effects In several who obtained subjective benefit no spirometric improvement was noted. Epinephrine and aminophylline produced decided spirometric changes

At times we have seen relief from asthma following intravenous or intramuscular injection of an antihistamine. However, we cannot be sure that this was not due to the sedative effect of the drug

The relative inefficiency of the antihistamines in asthma has raised the question of the presence of a mechanism in asthma which may differ from that in nasal allergy or urticaria. One cannot deny the possibility of this. On the other hand, the failure to respond may merely signify the release of an excessive amount of histamine which cannot be combated by the amount of antihistamine the patient is a[illegible] to tolerate Our experience with antihistamine ae[illegible] [illegible]nds to support the second explanation We have [illegible]nd that aerosols of

antihistamines, such as Pyribenzamine, are frequently effective in asthma. The amount which some patients require is so small that it is actually only a fraction of what is customarily taken by mouth. But the concentration reaching the bronchial tissues from the aerosol may be several times that reaching the same tissue after the drug is absorbed from the digestive tract.

Individual Drugs—Results

An additional few words of caution are indicated before discussing the individual drugs. The reader should bear in mind that not all reports are based on the same criteria and that most of the variables discussed in this and the preceding chapter may enter into the interpretation of any report. Also, for purposes of practicality and brevity, the number of reports for each drug had to be kept to a reasonable few. The choice of articles was influenced by a number of considerations which have necessitated the omission of many sources which were as good as or better than the ones included.

Antergan—This was the first of the present antihistamine series to be used therapeutically. It was introduced for clinical use in France in 1942 and was employed in Europe as the only antihistamine until Neo-Antergan supplanted it in 1945. Antergan is an active drug, but it has a high toxicity and is not well tolerated by man. Although we had the drug from France since 1945, our experience with it has been confined solely to experimental work in the laboratory.

Gaté (215) and [illegible]workers reported good results in a series of pa[illegible]no had hay fever, perennial rhi-

nitis, asthma or dermatoses. Decourt (125) obtained variable results in asthma and hay fever. Celice and his associates (80) reported satisfactory results in asthma and other allergic manifestations.

Antistine.—This drug was first introduced in Switzerland in 1946. Since then it has been used in some parts of Europe and also in this country. Milligram for milligram it is one of the least potent of the current marketed drugs, approximating in this respect only one other marketed drug, Neohetramine. Antistine has only a slight sedative effect, hence larger doses are usually tolerated. Our experience with this drug indicates that it is too weak for general use and that doses of at least 100–200 mg are required to produce fairly consistent effects. We have confined its use primarily to those patients who have a great tendency to be sedated by virtually all antihistamines In such instances, Antistine may be helpful. It should not be inferred that this compound causes no undesirable reactions, with large doses, and in some persons with moderate doses, sedation or gastrointestinal irritation results Antistine eye drops are often beneficial in allergic conjunctivitis

Schindler (480), in 1946, reported encouraging results with this drug in asthma Gay and his associates (219) (Baltimore) compared eight antihistamines clinically and concluded that the potencies of seven were virtually the same. The exception was Antistine, for which twice the dose was required. Kallos (293) found the drug valuable in allergic rhinitis and other conditions, but *neither orally* nor hypodermically was it effective in asthma Frei and Walterspiel (198) re-

ported good results in nasal allergy, but in asthma the effect was weak. It must be emphasized that most of the European observers, at least at the time they issued their reports, had no basis for clinical comparison with more potent antihistamines. To one who has not tried any other antihistamine Antistine may appear a very desirable addition to the therapy of allergy. The Friedlaenders (201) compared Antistine clinically with Pyribenzamine. They found a response in 59 per cent of patients with allergic rhinitis, using doses of 50–100 mg. However, most patients who tried both drugs preferred Pyribenzamine.

Benadryl.—This was the first American antihistamine to be marketed. It gives satisfactory results in a large percentage of patients but has the disadvantage that it is often too sedative. Although some of the later drugs are frequently more effective in nasal allergy, Benadryl has established a great popularity because of its priority. In some instances Benadryl may be preferred to other drugs either because sedative action may be desirable or because its anticholinergic action may be of advantage in conditions such as asthma. In comparing this drug with Pyribenzamine and Neo-Antergan in a series of patients we (34) found that the latter two were more effective.

The findings on this drug by various authors differ somewhat. Thus, Koelsche and his associates (311) (Rochester, Minn) reported that 75 per cent of 52 patients with uncomplicated hay fever obtained 50 per cent or more relief. Of 19 patients with asthma associated with hay fever, 74 per cent obtained relief. In

other asthmas, however, only four of 12 benefited. These findings agree fairly well with those of Eyermann (162) in St. Louis. During the 1945 season he observed relief in 67 per cent of hay fever patients and in 31 per cent of the asthmatics who had mild wheezing. Approximately the same results were obtained by Waldbott (555) in Detroit. Levin (334) (Detroit) obtained a 59 per cent incidence of relief in hay fever during the 1945 season and noted that, although allergic asthma was benefited, infectious asthma was not helped and four cases of asthma were aggravated.

Less encouraging results have been reported by others. Engelsher (155) reported that relief occurred in only about one third of his hay fever patients and in virtually no patients with asthma. In reporting the first trial of the drug in children during 1945, Logan (355) found that it was not very effective in asthma. Our early impressions of the poor results in asthma, reported in 1945 (185), have been corroborated by subsequent experience. The results obtained in asthma by McGavack and associates (366) are better than those of other workers. They believe that this is due to their custom of giving the drug continuously. It is interesting to note that they obtained improvement in four of eight cases of cardiac asthma.

Chlorcyclizine.—This drug is marketed under two trade names, Di-Paralene (Abbott Laboratories) and Perazil (Burroughs Wellcome & Co.). The compound was presented to one of us (S.M.F.) almost simultaneously by the two pharmaceutical houses, early in 1948. It is moderately effective in allergic manifestations, but its

action is not as consistent as that of some of the other potent antihistamines. Its chief advantage is the tendency to prolonged action, which in some instances results in relief lasting six to 15 hours. This prolonged action is particularly useful in cases in which morning or night symptoms may be prevented by a bedtime dose. Unfortunately, this long-lasting effect is not always present. The average dose in our experience is 50–100 mg In some patients the onset of effect is longer than that with other antihistaminic drugs. As with all the antihistamines, beneficial results in asthma were rarely obtained.

In the 1948 and 1949 hay fever seasons in Chicago, in one series we (179) found that this drug helped 46 of 87 desensitized patients (when antihistamines were required) and 16 of 38 patients who were not desensitized. In addition, the effect of the drug was more complete in desensitized patients than in those not desensitized. In perennial rhinitis 18 of 43 patients were benefited. Cough was benefited in four of eight patients, but only three of 36 asthma patients were relieved The toxic effects were as a rule mild and infrequent.

The first clinical report on this drug was presented by Jaros (288) who was associated at the time with Burroughs Wellcome & Co He found that in Eastern New York State, during the 1948 season, 22 of 23 patients with seasonal hay fever were improved, while 18 of 21 patients with perennial rhinitis were relieved. He recommended one dose of 25 mg. in 24 hours He concluded that "clinical experiments indicate greater efficiency and less toxicity than with Pyribenzamine." In

view of the small number of patients, the mildness of the season and the locale of the study on hay fever patients we feel that this enthusiastic report constitutes a hazardous opinion. Brown and his co-workers (64) of Boston also felt that chlorcyclizine was the most effective of all the antihistamines they had studied.

A report of the Committee on Therapy of the American Academy of Allergy (99) summarized the findings for 588 patients treated by nine members, representing New York, Detroit, St. Louis, Baltimore, San Diego, Chicago and Buffalo Relief in hay fever (50 per cent or more) was obtained in 55 5 per cent of 329 patients, while 38 4 per cent of 130 patients with nonseasonal rhinitis were benefited. The incidence of improvement in asthma was 12 8 per cent. The duration of action of this drug varied, but in a large percentage it was considerably longer than that of other antihistamines The incidence of side effects was not great, and the average dose was 50 mg given two to three times daily

Chlorothen.—This is the chlorinated analogue of Thenylene or Histadyl It is an effective drug in allergic manifestations, but it does not differ materially from other good antihistamines The usual dose is 50 mg, but often 25 mg. is sufficient. Duration of action is about the same as that of most of the other antihistamines. In the 1947 ragweed and mold season we (176) noted that 70 per cent of 182 patients obtained relief. Of 40 patients with perennial vasomotor rhinitis 62 per cent improved, and of 20 with allergic cough six were benefited. In asthma, improvement was seldom evident. Toxicity is moderate, comparable to that of Pyribenzamine.

Chlor-Trimeton.—Introduced in the summer of 1949, this drug is a chlorine analogue of Trimeton, a drug marketed by the same firm for some time. Although there were no published reports of its clinical use at the time of marketing, much was claimed for Chlor-Trimeton by the manufacturer because it is more potent milligram for milligram than any other antihistamine. This is true, the effective dose being 4–8 mg. However, our experience indicates that in these doses it is no more, and probably less, potent than some of the other antihistamines in larger doses. In larger doses the same difficulties arise with Chlor-Trimeton as with the other drugs, for example, 12 mg. is rarely tolerated well. Thus, the advantage of the small dose effectiveness becomes a benefit only to the producer since the consumer rarely considers milligrams—he takes pills, and they are all about the same and all about equal in cost.

Eisenstadt (149) reported that this drug used as adjunct therapy to desensitization gave relief to 51 of 60 hay fever patients. It also helped nine of 13 patients with perennial allergic rhinitis.

The Committee on Therapy of the Academy of Allergy (99) tabulated combined experience of 11 members who treated a total of 990 patients with Chlor-Trimeton. The localities represented included New York, Baltimore, Boston, Detroit, Chicago, St. Louis, Omaha, San Diego and Buffalo. Of 715 patients with hay fever 61.3 per cent showed improvement (50 per cent or more). Among 151 patients with perennial rhinitis 52.5 per cent were benefited. In asthma the incidence of relief was 24.6 per cent. Duration of effect

was about the same as that with other drugs. Moderate to severe side effects were noted in 7.5 per cent of patients, although a much larger percentage experienced mild untoward symptoms. The usual dose was 2–4 mg given three or four times daily. Larger doses offered little advantage.

Decapryn.—This is a potent antihistamine, both in therapeutic effectiveness and sedative action. The average therapeutic dose is 25 mg., although some patients require as little as 12.5 mg while others need 50 mg. or even more In these doses we (183) found that 75 per cent of hay fever patients in the Chicago area, most of whom had the ragweed or mold type, were benefited during the 1947 season. In perennial rhinitis 19 of 34 were helped. Although the incidence of good results with Decapryn in our experience has been no greater than that with several other good antihistamines, the drug is sufficiently different from many others to select it for use when others fail. This is particularly true when decided sedative action is desirable.

Sheldon and his associates (499) administered Decapryn to 84 hay fever patients and found it effective, particularly for the sneezing symptoms. Wheezing was satisfactorily controlled in more than half the cases. The doses varied from 6.5 to 100 mg. In 140 patients with clinical allergy Brown *et al.* (65) used doses of 12.5–25 mg and of 50 mg. in some In asthma, 27 of 41 were benefited.

Diatrin.—Little has been published on clinical results with this drug. Our own limited experience with Diatrin indicates that it is a moderately effective drug but has

ephedrine and aminophylline will be discussed in Chapter 9.

Neo-Antergan.—This drug is effective in nasal allergy but, in our experience, not quite as effective as Pyribenzamine (34). The side reactions are moderate, although there is considerable tendency to gastrointestinal irritation The customary dose is 50–100 mg. Neo-Antergan is marketed both in Europe and in this country and was first marketed in France.

Our laboratory and clinical experience with this compound began in 1945, when through the kindness of Dr. Bernard Halpern of Paris and the Rhone-Poulenc Company we received a generous supply. There have been a number of reports, experimental and clinical, on this compound, emanating particularly from Europe but recently also from American sources Decourt (123) found that Neo-Antergan was more effective and less toxic than Antergan Southwell (510) found it very good in 15 hay fever cases (England) but obtained no benefit in 25 cases of asthma In a comparison of Pyribenzamine, Neo-Antergan and Benadryl, we (34) found Neo-Antergan second in effectiveness. Loveless and Dworin (360) reviewed the literature on the therapeutic and toxic action of a number of antihistamines, averaging the results of all investigators, and found that Neo-Antergan stood in about the middle of the list They then called attention to the dangers of such an evaluation since the standards and interpretations differ with each worker. They compared the findings in 113 of their own patients and found that while Pyribenzamine and Trimeton were at the top of the list, Neo-

ephedrine and aminophylline will be discussed in Chapter 9.

Neo-Antergan.—This drug is effective in nasal allergy but, in our experience, not quite as effective as Pyribenzamine (34). The side reactions are moderate, although there is considerable tendency to gastrointestinal irritation. The customary dose is 50–100 mg. Neo-Antergan is marketed both in Europe and in this country and was first marketed in France.

Our laboratory and clinical experience with this compound began in 1945, when through the kindness of Dr. Bernard Halpern of Paris and the Rhone-Poulenc Company we received a generous supply. There have been a number of reports, experimental and clinical, on this compound, emanating particularly from Europe but recently also from American sources. Decourt (123) found that Neo-Antergan was more effective and less toxic than Antergan. Southwell (510) found it very good in 15 hay fever cases (England) but obtained no benefit in 25 cases of asthma. In a comparison of Pyribenzamine, Neo-Antergan and Benadryl, we (34) found Neo-Antergan second in effectiveness. Loveless and Dworin (360) reviewed the literature on the therapeutic and toxic action of a number of antihistamines, averaging the results of all investigators, and found that Neo-Antergan stood in about the middle of the list. They then called attention to the dangers of such an evaluation since the standards and interpretations *differ* with each worker. They compared the findings in 113 of their own patients and found that while Pyribenzamine and Trimeton were at the top of the list, Neo-

results, the effectiveness of Neohetramine was considerably inferior to that of Pyribenzamine and several other antihistamines Waldbott and Borden (556) of Detroit obtained 38 per cent good results in 165 hay fever patients, while 17 per cent of 75 patients with asthma were benefited

Perazil.—See chlorcyclizine.

Phenergan—This is an interesting antihistamine which is only now being marketed in this country. Through the kindness of Dr. Halpern and the Rhone-Poulenc Company of France we obtained a substantial quantity of this compound several years ago and made rather complete laboratory studies and some clinical trials with it. This antihistamine has distinct individual characteristics It is highly sedative, perhaps the most sedative of all the clinically used antihistamines. Therapeutically it is very effective, but its sedative action frequently limits its use in large doses or even in moderate doses in ambulatory patients Another feature of this drug is its prolonged action. We found it most useful in those patients in whom a bedtime dose would often be sufficient to prevent morning symptoms of nasal allergy. In many instances one daily dose was sufficient. Because of our limited supply of the drug we have confined its use to special cases It is possible that a more thorough clinical trial would elicit further desirable qualities of this drug, but at any rate it is handicapped for general use by the tendency to pronounced sedation. The dose we have used most often is 25 mg

Halpern and Hamburger (254) reported that of 142 patients with hay fever (in France), 98 were totally re-

Antergan was of good but lesser potency in their series.

Neohetramine.—This is one of the two least potent of all marketed antihistamines. With 50–100 mg. doses we (32) obtained a fair incidence of relief in hay fever, but the degree of relief was not as good as that with many other drugs. The main advantage of this compound is the low incidence of side effects, the incidence being only 16 per cent with 100 mg. doses We feel that for full therapeutic results doses larger than 100 mg. would have to be used, and with larger doses toxicity may be as high or higher than it is with some other antihistamines. Our recommendation is that the use of this drug be confined to those patients who do not tolerate most of the antihistamines but do respond to small or moderate doses of Neohetramine.

The Friedlaenders (207) of Detroit used doses of 50 or 100 mg., more often the latter, and obtained effect in 64 per cent of hay fever patients and in 52 per cent of patients with perennial rhinitis. Criep and Aaron (108) in Pittsburgh claimed that in allergic rhinitis Neohetramine was effective in 80 per cent of patients, while in seasonal hay fever they found it effective "in the same percentage that Feinberg obtained with Pyribenzamine." Needless to say, such comparisons are invalid. Feinberg tried Pyribenzamine in one season in Chicago while Criep and Aaron tried Neohetramine in another season in Pittsburgh. The standards of a classifiable "good" result may differ with the two observers. Indeed, when Feinberg compared Neohetramine with Pyribenzamine in the same practice, in the same locality, in the same patients, using the same gradation of

using Pyribenzamine in the form of nasal spray in some cases of resistant nasal allergy. An aerosol of Pyribenzamine has been helpful in some cases of asthma.

Arbesman and his collaborators (17) obtained improvement in 75 per cent of patients with all types of allergic rhinitis and in 85 per cent of seasonal hay fever patients. They also claimed results in 47 per cent of 159 asthmatics (14). They concluded that Pyribenzamine was more effective and less toxic than Benadryl. Bernstein, Rose and Feinberg (34) in a comparative study of Benadryl, Neo-Antergan and Pyribenzamine found Pyribenzamine the most effective. Loveless and Dworin (360), in a comparative study of several drugs, found Pyribenzamine and Trimeton the most effective. In analyzing their results with Pyribenzamine and Benadryl, Engelsher (155) and Ratner (434) concluded that the value of the antihistaminic drugs has been overestimated. We concur in general with their statements but feel that Engelsher's claim of relief in only one third of his hay fever patients is at variance with our experience and that of most allergists.

Pyrrolazote—This drug has good clinical potency. In two series of hay fever patients of all types in the 1948 and 1949 seasons, 63 per cent of the 174 patients obtained symptomatic relief. The usual dose is 50 mg., and with this dose side effects are moderate. However, for the 100 mg dose side effects were frequent and often severe The results in asthma were negligible. In vasomotor rhinitis the incidence of effective results was 54 per cent.

Tagathen—See chlorothen.

using Pyribenzamine in the form of nasal spray in some cases of resistant nasal allergy. An aerosol of Pyribenzamine has been helpful in some cases of asthma.

Arbesman and his collaborators (17) obtained improvement in 75 per cent of patients with all types of allergic rhinitis and in 85 per cent of seasonal hay fever patients. They also claimed results in 47 per cent of 159 asthmatics (14) They concluded that Pyribenzamine was more effective and less toxic than Benadryl. Bernstein, Rose and Feinberg (34) in a comparative study of Benadryl, Neo-Antergan and Pyribenzamine found Pyribenzamine the most effective Loveless and Dworin (360), in a comparative study of several drugs, found Pyribenzamine and Trimeton the most effective. In analyzing their results with Pyribenzamine and Benadryl, Engelsher (155) and Ratner (434) concluded that the value of the antihistaminic drugs has been overestimated. We concur in general with their statements but feel that Engelsher's claim of relief in only one third of his hay fever patients is at variance with our experience and that of most allergists

Pyrrolazote—This drug has good clinical potency. In two series of hay fever patients of all types in the 1948 and 1949 seasons, 63 per cent of the 174 patients obtained symptomatic relief. The usual dose is 50 mg., and with this dose side effects are moderate. However, for the 100 mg dose side effects were frequent and often severe. The results in asthma were negligible. In vasomotor rhinitis the incidence of effective results was 54 per cent.

Tagathen—See chlorothen.

asthma 13 obtained benefit. Sternberg and Gottesman (520) observed relief in only 18 of 41 hay fever patients, four of 26 asthma patients, and none of six patients with perennial vasomotor rhinitis.

Trimeton.—Our experience with Trimeton indicates that it is an effective antihistamine. The early claims that it is the most effective and least toxic antihistamine have not been in agreement with our observations. As a matter of fact, we have had more complaints of sedation from therapeutically effective doses of Trimeton than we had from Pyribenzamine and other potent antihistamines The usual effective dose is 25–50 mg., although a large percentage of patients do not tolerate the higher dose. We have never used Trimeton in doses comparable to those of Pyribenzamine used in severe allergic syndromes, because it was our feeling that tolerance would be poor.

Brown (63) (Boston) reported relief with this drug in 90 per cent of hay fever patients and in 80 per cent of patients with mild intrinsic asthma. In three other reports (232, 479, 580), each of which tabulates a group of from 15 to 34 hay fever patients, relief was observed in from 66 to 90 per cent Loveless and Dworin (360) found that Trimeton compared favorably with Pyribenzamine in their study. The Committee on Therapy of the American Academy of Allergy (98) reported tabulated results from a number of investigators and stated that Trimeton "compares very favorably with the other antihistamines on the market." In a total of 908 hay fever patients 65 per cent had good or excellent results. Of 956 patients with perennial vasomotor rhinitis,

CHAPTER ~

Dermatoses

THE USE OF the antihistaminic drugs in dermatology came soon after drugs, nontoxic enough to be used in man, were available. Early reports on Antergan (80, 215) in urticaria and pruritus were encouraging. As clinical reports have accumulated, the role of these agents has become better defined. Probably the most important and one of the most constant effects of the drugs in lesions of the skin is the antipruritic effect. Many lesions are improved because the patient no longer scratches and causes secondary irritation and infection. Differences between the various drugs are not great, provided the proper dosage is used and this dosage is tolerated.

URTICARIA AND ANGIONEUROTIC EDEMA

Urticaria has probably been alleviated to a greater extent by these drugs than has any other disease. Drug therapy before the advent of these compounds was seldom satisfactory. In 1942 Antergan (80, 215) was shown to be quite effective in treatment, but knowledge

of these results was slow to reach this country. The first American reports of the clinical use of antihistamines dealt with urticaria (114, 115). Eighteen patients were treated, and in 11 there was complete disappearance of urticaria when 50 mg. of Benadryl was taken two to three times a day. In three of the patients 100 mg. four times a day gave improvement, while four received no relief. It was noted that while under treatment a nonpruritic wheal appeared at times.

Generally speaking, acute urticaria responds better to the antihistamines than does the chronic type. The effective dose of the antihistamine depends largely on the severity of the urticarial dermatosis. The mild cases usually respond well to 50 mg. doses of Pyribenzamine, whereas the severe ones, particularly those associated with deep lesions, require 100–200 mg per dose, or the equivalent of other antihistamines The duration of effect from each dose also varies with the severity of the syndrome as well as with the size of the dose. Thus, in very severe cases, the effect frequently lasts only two to three hours after each administration. In a large percentage of cases, cyclic fluctuations in the urticarial lesions occur, hence the actual effectiveness and its duration must be interpreted with great care. The itching is most often the manifestation which is relieved, whereas the edema is more resistant to the drug. However, even though the preformed edematous areas are affected very little by the antihistamine, repeated use of the drug may limit the degree of edema and erythema in new lesions.

Angioneurotic edema is closely related to urticaria and may be regarded as an anatomic variant of the same

manifestation. Indeed, lesions of both urticaria and angioneurotic edema are often present in the same patient at different times or at the same time. Angioneurotic edema shows a slower and less complete response to the antihistamines, primarily because itching is not a factor and because the edema is more infiltrative and is apt to involve muscles and joints. Larger doses are often required, and other therapy may have to be administered in addition to the antihistamine. For edema in vital areas, such as the larynx, vasoconstrictors, particularly epinephrine given hypodermically, are still the therapies of choice.

Morbilliform, erythematous and similar itching rashes, often due to drugs, respond favorably to the antihistamines.

Antistine, as reported by Friedlaender and Friedlaender (201), helped 10 of 20 patients with urticaria. Less than half as many side effects were noted with Antistine, compared with Pyribenzamine. Schindler (480) and Overton (414) obtained very good results using Antistine This drug generally produces fewer side effects than others in equivalent doses, but if the dose is increased to give equal therapeutic results, the incidence of side effects also increases. We use this drug when the patient is not able to tolerate the more potent drugs.

In 1945, we (185) reported that relief was obtained in urticaria using Benadryl orally. O'Leary and Farber (409) found that of 35 patients with acute urticaria, 20 were completely relieved, 12 were improved and three were *not* affected Forty-eight of 75 patients with chronic urticaria had relief; there were 10 complete failures in

and Borden (556) treated 21 patients with Neohetramine, relieving 12. Again, as with Antistine, the incidence of side effects with Neohetramine is low, although the potency is also low.

Halpern and Hamburger (254) used Phenergan in 123 patients with urticaria and obtained relief in 88 per cent of the group Dosage was 25 mg. one to four times daily. We find this drug is highly potent and has a longer duration of action than most others, but the high incidence of side effects even at fairly low dosage precludes its routine use Given at bedtime it may constitute desirable antihistamine medication.

Arbesman and his associates (17) were the first to use Pyribenzamine clinically. In 154 patients with urticaria 83 per cent were helped. Our results (186) were similar Twenty-three of 24 patients were relieved by Osborne and associates (412) whereas Baer and Sulzberger (22) noted relief in only 50 per cent of patients. We find Pyribenzamine to be one of the more effective drugs in the treatment of this condition. We have frequently observed that failure of response is, in some cases, due to inadequate dosage.

Although extensive clinical reports on its use are lacking, we (176) find chlorothen (Tagathen) to be effective in the treatment of urticaria, ranking among the more potent drugs in the series. Thephorin was highly effective in a series of patients treated by Kesten and Sheard (309). In other series, 60 per cent (109) and 75 per cent (336) of patients obtained relief. The advantage of this drug is that it produces less sedation than many of the other drugs, although other side ef-

administration of the agent and commonly consists of an itching rash, urticaria and angioneurotic edema, arthralgia with or without evidently swollen joints and fever. Albuminuria is not unusual and more serious renal, vascular or nervous system lesions may be present at times. The antihistamines will benefit most patients with serum type reactions. The itching and urticaria are helped most, the joint manifestations are usually more resistant. The fever may also be modified but is not consistently affected. The arthralgia and fever can usually be relieved with salicylates (80, 308, 550). Small doses of the antihistamines are rarely effective in this syndrome, and most treatment failures result from inadequate dosage Usually not less than 100 mg. of Pyribenzamine given approximately every four hours is required, and the very severe cases may require 150–200 mg quantities Sometimes oral medication fails because of poor absorption, in such cases the antihistamine may be given parenterally

It is important to bear in mind that, as in other allergic manifestations, the effect of the antihistamines is palliative only The best that can be expected from these drugs is comfort for the patient and control of the disease As soon as the drugs are discontinued the manifestations recur, until such time as the natural evolution of the disease has caused its termination. On the average, "serum sickness" will last from a few days to two or three weeks with or without medication. In some instances the syndrome lasts a month or more, in others it may persist for several months in modified form. It is not certain what the mechanism of the persistence of the

sponse to a reacting antigen is only slightly reduced. Nevertheless, one must bear in mind the possibility that a normally minimal scratch reaction to an antigen might be entirely obliterated under the influence of an antihistamine. The drug chosen to treat dermographism depends on factors previously discussed for urticaria. It is our impression that Benadryl is more effective for this purpose than many other drugs, its advantage possibly being its additional antiacetylcholine action. Drugs described in the literature include Benadryl (185), Tagathen (176), Histadyl (Thenylene) (182), Pyribenzamine (23, 308) and Thephorin (309).

Atopic Dermatitis (Eczema)

In the treatment of atopic dermatitis, variously known as eczema and neurodermatitis, the antihistamines have not been as satisfactory as they have been in the urticarial dermatoses. They are of considerable help in the management of this disorder, but seldom do they cause complete regression and in many patients no relief whatever is obtained. The principal action of the drugs seems to be the ability to alleviate pruritus. However, when this is accomplished and scratching is minimized, secondary infection and traumatic injury clear up more rapidly and the lesions become less disfiguring. Sometimes this makes it easier to discover the etiology, because the lesions regress more readily when the etiologic factor is eliminated and irritation from scratching is absent. Certainly other factors in the treatment of atopic dermatitis must not be overlooked in favor of the antihistamines if the results are to be satisfactory.

parisons should not be made, because the number of patients is too small to give significant results.

Schwartz, Levin and Wallman (483), reporting on the use of Histadyl (Thenylene), stated that 50 per cent of their patients with allergic eczema benefited. Marin, Foisy and LeClerc (379) treated 13 patients with Neo-Antergan for one to two months and found this drug to be of little value. Phenergan, used by Halpern and Hamburger (254), relieved pruritus to some extent in a few of 17 patients with chronic eczema.

Pyribenzamine was of practically no value in the treatment of atopic dermatitis, according to Baer and Sulzberger (22) We (186) obtained relief of the pruritus associated with the atopic dermatitis Using Pyribenzamine orally, 100–400 mg daily, Osborne *et al.* (412) relieved the pruritus about 50 per cent in 19 of 30 patients Kesten (308) helped 27 of 40 patients. In 1947 we (181) reported on the use of a 2 per cent ointment of Pyribenzamine to relieve the itching of atopic dermatitis and other conditions. This ointment may be used provided the area to be treated is not great, for absorption does take place and overdosage is possible, furthermore, treatment of a large surface area is not practical in ambulatory patients. The use of such an ointment, with or without the simultaneous use of an oral preparation, gives relief to a large percentage of our patients Sulzberger, Baer and Levin (530) found no beneficial effects from ointments in this disease. (For further discussion of topical application see Chapter 9.)

We (176) have found chlorothen (Tagathen), given orally, to be fairly effective in this condition.

Benadryl indicated that this drug is unsatisfactory in the treatment of contact dermatitis. However, McGavack *et al.* (367), who applied Benadryl topically in a 2-5 per cent ointment, reported that 20 of 25 patients with poison ivy obtained complete relief and five improved. Rosenberg and Blumenthal (463), using Benadryl intravenously, were able to relieve the pruritus of four patients with poison ivy.

The report of the Committee on Therapy of the American Academy of Allergy (99) showed that chlorcyclizine did not help two patients with contact dermatitis but that Chlor-Trimeton gave 50 per cent or more relief in 11 of 15 patients. Histadyl (483) and Neohetramine (207) have also been reported to give some relief in this condition

Pyribenzamine failed to influence the symptoms or lesions when given orally in one series of 15 patients (412). Sulzberger *et al.* (530) found Pyribenzamine cream to be effective in only a small minority of cases of contact dermatitis In artificially induced poison ivy, Tweedall and O'Connor (542) found that Pyribenzamine given orally did not prevent the dermatitis and only moderately relieved the itching and burning The Committee on Therapy of the American Academy of Allergy (98) observed that Trimeton was effective (good and excellent results) in only 18 per cent of 17 cases of contact dermatitis

PRURITUS

The effect of the antihistamines on pruritus has been discussed in relation to the various disease entities con-

of our patients with this type of pruritus have been helped, but others responded poorly. Good results using Pyribenzamine to treat the pruritus of chickenpox have been reported by Silverman (504).

histamines with partial to complete relief of symptoms. In 1946, Gastineau and Leavitt (214) reported the use of Benadryl to treat urticaria and angioneurotic edema caused by insulin in a diabetic who was sensitive to insulin. The urticaria was controlled by oral administration of 250–350 mg of Benadryl, but the angioneurotic edema persisted Later, the same authors (325) suggested combining the Benadryl with the insulin before injection. Carryer and Koelsche (78) gave Benadryl orally to help accomplish rapid desensitization to liver extract in several cases of allergy to the latter Hunter and Dunlop (281) also reported the use of antihistamines in treatment of sensitivity to liver extract and insulin

The use of the antihistamines to prevent local and constitutional reactions in patients undergoing specific desensitization therapy for hay fever or other allergic manifestations deserves some comment. This procedure is rarely indicated and should be used only in those patients in whom constitutional reactions frequently occur. Only moderate increments in the dose of the desensitizing antigen should be made, since large increments, such as double or triple the dose, may result in serious reactions despite use of the antihistamine As a rule, the best time to administer the drug orally for this purpose is one hour before the injection of the antigen.

DISEASES OF THE EYE

The use of these drugs in the treatment of diseases of the eye of known allergic etiology has been generally satisfactory Oral administration is often useful in cases

of itching and lacrimation associated with seasonal hay fever, but at times topical application is necessary. Bourquin (47) reported in 1946 on the use of Antistine solution locally in cases of allergic conjunctivitis and palpebral eczema. He also obtained symptomatic relief in some cases of chronic conjunctivits, phlyctenular conjunctivitis, nonbacterial conjunctivitis, keratoconjunctivitis, scleritis, iridocyclitis, Reiter's syndrome and other eye conditions in which etiology is obscure, unknown or known and not related to allergy. Harris, McGavack and Elias (265) found that whereas the oral use of Benadryl had no effect on pupillary size in 20 subjects, topical application of a 0.5 per cent solution caused an atropine-like dilatation of the pupil in 48 of 60 subjects, decreasing visual acuity in 12. These findings create a valid objection to the use of this particular drug in the eye.

Hurwitz (282) reported on the use of Antistine locally in ocular allergy. Eighty-four per cent of 50 patients experienced subjective symptomatic improvement, the greatest benefit occurring in ragweed hay fever patients. Leopold, Dean and Blazar (333) found that in rabbits with experimental anaphylactic uveitis, Pyribenzamine given systemically before the challenging dose prevented the reaction, but if given after or at the same time, it failed to prevent the reaction. They believed that this indicates that Pyribenzamine may be useful in the prevention of human sympathetic ophthalmia and of endophthalmitis phacoanaphylactica.

Daily and Daily (116) used a combination of 0.5 per cent Antistine and 0.025 per cent Privine in 100

patients with various types of conjunctivitis. Relief from burning, itching, photophobia and lacrimation was obtained. Stocker (522) used Antistine eye drops in 0.25–0.5 per cent concentration and Histadyl drops and ointment in 0.5 per cent concentration. He claimed improvement in cases of allergic dermatitis, blepharitis, conjunctivitis, vernal catarrh, episcleritis, recurrent erosion, iritis, herpes corneae and phlyctenular conjunctivitis.

It must again be emphasized that these drugs are only palliative and that prolonged use may cause irritation or contact sensitivity (401). In some patients, topical use of these drugs in the eye is not possible even initially because of too much irritation.

Collagen Diseases

The findings of Rich and Gregory (444) that periarteritis nodosa is probably due to a hypersensitivity reaction and that lesions resembling rheumatic fever, serum sickness and the collagen diseases could be produced in rabbits by the injection of a foreign protein (443) have stimulated research to find a preventive or curative treatment for these diseases. Both positive and negative results have been claimed by experimenters using antihistaminic drugs. In 1945 Reubi (440) claimed that the antihistamines prevented nephritis ordinarily produced in rabbits by antiserum. Benadryl and another antihistaminic drug were reported by Kyser *et al.* (316) to prevent rheumatic-like lesions in the myocardium of serum-injected rabbits. However, MacGregor and Wood (368), using Neo-Antergan and Benadryl, were unable to reproduce these results. Clinical studies

on the use of these drugs in periarteritis nodosa generally have been without results (281, 361), but in one case recovery was reported (531). Lynch's (361) results were "inconclusive but somewhat encouraging" in lupus erythematosus. Stephens and Holbrook (518) reported good results in two of three patients with disseminated lupus erythematosus using Benadryl Hunter (281) had two patients with dermatomyositis who were unimproved. Four patients with scleroderma did not respond (409), whereas among nine patients with acrosclerosis, seven obtained some temporary reduction in edema, the effect being sustained in only two. In a small series of patients, treatment of rheumatic fever with these drugs has been a failure (545).

Thus, it is obvious that the status of antihistamines in the treatment of this group of diseases is not very satisfactory. Our own experience in cases of acute rheumatic fever, nephrosis, disseminated lupus erythematosus and periarteritis nodosa has confirmed this. In one patient with dermatomyositis large doses of Pyribenzamine produced temporary improvement in erythema and itching.

Tuberculosis

The effect of the histamine antagonists on tuberculosis and the tuberculin reaction has been investigated in the guinea pig and in man. In man, at least five reports (110, 209, 238, 306, 549) indicated that there was no effect on the tuberculin reaction, while another report (236) showed a depression of the reaction Judd and Henderson (291) treated 30 patients with pulmonary and nonpulmonary tuberculosis with Benadryl, Pyri-

benzamine, Thephorin or Neohetramine in daily doses of about 300–400 mg. The results were encouraging, indicated by temperature drop, sputum and improvement in weight, appetite and x-ray findings. Patients who started therapy earliest in the course of the disease obtained the best results Mantoux reactions were also diminished Millner and Hurst (396) treated 28 tuberculous patients with Neo-Antergan during the day and Phenergan at night for a period of several months. The results, assessed by x-ray, sputum volume, sedimentation rate and weight, were not striking, although some benefit might have been present, possibly owing to the atropine-like and sedative actions of the drugs. Certainly we might conclude that the value of these drugs in the therapy of tuberculosis is far from proved and that much larger series of cases must be observed.

THE COMMON COLD

The promotion of the antihistamines in the treatment of the common cold and the permission granted by the Food and Drug Administration for over-the-counter sale of several of the antihistamines have resulted in extensive claims in lay advertising. The quantities of the antihistamines used in colds have already exceeded those used in allergic conditions (513) Since the promiscuous and unsupervised use of these drugs is bound to result in many serious toxic effects and accidents, it becomes necessary to examine the evidence on which the claims for their employment is based.

Basis for trial of antihistamines in colds.—The circumstances which have suggested the use of these drugs

in treatment of the common cold are several. Since rhinorrhea and sneezing are symptoms common to both allergic rhinitis and colds, it was but natural to suppose that these symptoms in colds also were on an allergic basis or, at any rate, that they might respond to the antihistamines. Another pertinent basis rests on the claim that in some stages of virus infection in colds allergy plays a prominent role (196a). Most authorities in the field are not willing to agree on the role of allergy as an important feature in the common cold. Even if allergy to virus does play a part it does not necessarily signify that antihistamines will ameliorate that type of allergy. Indeed it has been definitely shown that the allergic manifestations of bacterial or other infectious disease are not helped by the antihistamines. This can readily be explained by the fact that histamine does not play a significant role in this type of allergy.

The finding of histamine in the nasal secretions of the common cold by Troescher-Elam, Ancona and Kerr (541) is often quoted in support of the allergic mechanism of colds. These workers made bioassays of the histamine of the nasal secretions in a small series of patients with colds and found that the quantities of histamine were about the same as those in allergic rhinitis. The technic of their method of dropping the extracted solution on the intestinal strip instead of in a bath is open to criticism. The amounts of histamine found were not excessively large. It is even possible that similar quantities might be found in normal nasal secretions if such controls were used. The findings of these workers have not been substantiated.

Perhaps the most impelling basis for the interest in the antihistamines in the common cold is a commercial one. A $100,000,000 annual business (513) constitutes more than a minor temptation Commercial interests were quick to appreciate the prospective market, especially in view of the fact that it has been definitely established that from 25 to 50 per cent of the population honestly believe that placebo tablets have been instrumental in stopping their colds.

Claims for successful treatment of colds.—Brewster was the first to present a series of patients whose colds had been treated with antihistamines. In his several studies (56–59), using Pyribenzamine, Thenylene, Neo-Antergan, Histadyl and Benadryl, he claimed that these drugs aborted the common cold in a high percentage of subjects, provided they were taken *in the first* few hours of symptoms. For the most part the patient made the diagnosis and very few control cases or placebo administrations were employed. Murray's (403) good results were also based on a diagnosis by the patient. Gordon (234) likewise claimed success in the treatment of colds with antihistamines and his criterion of a cold was the procurement of a negative culture.

The study of Arminio and Sweet (20) was more thorough Both prophylactic and treatment studies were made In the prophylactic group 300 subjects were given 50 mg of Neohetramine one to three times daily. Another group of 300 were given no antihistamines. Of the control group 19.7 per cent were free from colds, while of the antihistamine group 88 per cent were coldfree during the period of October to April. *In the treat-*

ports do not indicate proper control series and placebo therapy Few of them, either by history or observation, have taken cognizance of the possibility of allergy.

Failure of antihistamines in colds—Carefully conducted studies have recently been made which indicate that the antihistamines do not stop the common cold. Paton and his associates (416) reported an interesting study Ten subjects were given placebo tablets and 12, Neo-Antergan. They were instructed to take the medication in the first 24 hours of a cold and continue for two days The dosage used was 100 mg. three times daily. The patients' opinions were obtained. Of 10 taking placebos four benefited, while of 12 taking Neo-Antergan four benefited. The average duration of colds in both groups was slightly over six days. The physicians who examined the patients were asked to venture an opinion as to which patient was receiving the drug and which the placebo. Their guesses were correct 50 per cent of the time Admittedly this was a small series, but these investigators are continuing the study.

A carefully controlled series was observed by Shaw and Wightman (496). In the cold clinic of Cornell University Student Medical Clinic, 443 subjects were observed who had colds of no longer than 48 hours' duration To one-half of them placebos were administered while to the other half 50 mg of 2-phenyl-benzyl-amino-methylimidazoline hydrochloride was administered every four hours The patients were observed daily. Of those receiving the antihistamine 53 per cent thought they were benefited, while of those receiving the placebo 50 per cent regarded themselves improved

Fabricant (164), from a recent study of a group of medical and other professional students, has concluded that placebo medication gives as high a percentage of results as do the antihistamines.

In a report of the Council on Pharmacy and Chemistry of the American Medical Association (102) on this subject, suggestions were made for criteria for controlled studies on colds. Among the suggestions was the recommendation that direct virus inoculations be done. Feller and his associates (192) have approached the problem from this viewpoint. In one series of 49 volunteers, direct transmission of cold virus from the secretions of a patient with a cold resulted in about 60 per cent "takes" in each of three groups. The three groups comprised the following: those receiving Pyrrolazote, 50 mg. four times daily beginning just before inoculation, those receiving Neohetramine under similar conditions, and those receiving placebo tablets. Not only was the percentage of colds about the same, but the duration and severity of the symptoms were equal.

In another experiment these authors reported results obtained in 55 families who were under controlled observation and study. In 66 colds which were treated with antihistamines and in 218 which were not treated the duration and severity of the colds were about the same.

While our own observations are necessarily limited, they represent the experience of other allergists with whom we have discussed this subject. We believe they are of some significance. Almost since they were first available we have learned to use the antihistamines as a diagnostic agent to differentiate allergy from infection.

creased acid production (128). Experiments in man have been performed on normal controls who were given histamine and on patients with peptic ulcer. In a small group of hospital patients with peptic ulcer and acute gastritis, contrary to most published reports, we have obtained some benefit from the use of large doses (50 mg.) of Decapryn. We believe the results are due not to decreased acid secretion but more likely to the sedation, atropine-like action and local anesthetic action of this drug.

In gastrointestinal allergy the results have been variable; most reports have dealt with only a small number of cases (98), so that definite conclusions could not be reached. It is known that some patients are able to tolerate an allergenic food if they first take an antihistamine. We might conclude that trial is worth while, although elimination of a known offender, when feasible, is a better rationale.

Motion Sickness, Nausea and Vomiting

Although some of the commoner side effects of the antihistamines are nausea and gastric discomfort, it was noted by Gay and Carliner (217, 218) that, in patients susceptible to motion sickness, nausea and vomiting were often prevented by using Dramamine, the 8-chlorotheophylline salt of diphenhydramine. They reported that Dramamine prevented symptoms of seasickness in 132 of 134 men and completely relieved 187 of 195 men who were seasick. These results have been criticized by Tyler (543) who believed that control conditions were not adequate and that comparison with known

remedies such as hyoscine should have been made. Strickland and Hahn (526) found Dramamine effective in preventing airsickness in 71.3 per cent of 108 patients when 100 mg. of the drug was given preflight, whereas a placebo helped only 44.4 per cent of 108 patients. Simon and Seyler (505) believed that Dramamine causes too much drowsiness to be used safely by pilots. Such a side action would be a contraindication to the indiscriminate use of this drug by a person driving any vehicle. Chinn and Oberst (84) found Benadryl as effective as Dramamine in prevention of airsickness, while 8-chlorotheophylline alone gave only slight protection. Hyoscine plus Benadryl was more effective than any of the drugs alone. McEvedy (363) reported that pyranisamine maleate (Anthisan, Neo-Antergan) prevents seasickness as well as hyoscine does.

Carliner, Radman and Gay (76) used Dramamine to treat nausea and vomiting of pregnancy. Thirty-one of 43 patients were completely relieved in three hours with 100 mg. Dougray (132) used 100 mg. of pyranisamine maleate twice a day or 25 mg. of Phenergan three times a day in 94 cases of nausea and vomiting. Eighty-three per cent of patients obtained complete relief, 4 per cent improved and 13 per cent were considered treatment failures. Finch (193) treated 29 patients with nausea and vomiting of pregnancy and 21 who had similar effects from synthetic estrogens with Benadryl and Histadyl with good results. One drug was as effective as the other. The use of antihistaminic drugs to treat the nausea and vomiting due to streptomycin therapy was reported by Bignall and Crofton (38) in four

cases The nausea and vomiting were relieved, but the associated giddiness was not affected. Stocker (522) found Dramamine effective in preventing postoperative nausea and vomiting following cataract extraction. Chen and Ensor (82), studying apomorphine-induced emesis in dogs, showed that Benadryl is an effective antiemetic and that Dramamine in doses representing equivalent amounts of diphenhydramine is equally effective, whereas 8-chlorotheophylline is ineffective. Phenobarbital and atropine were effective only in hypnotic doses. These authors believed that the probable site of action is the vomiting center or associated pathways.

Results in the use of the antihistamines to treat morphine-withdrawal symptoms (305) might be explained on their central action on the vomiting center.

Radiation Sickness

Believing that the symptoms of radiation sickness are caused by an increase in histamine release, Lofstrom and Nurnberger (354) treated 18 cases using oral and intravenous doses of Benadryl. Improvement was noted in all cases, and the mental condition of the patients also showed decided improvement. Court Brown and Hunter (103) did not obtain such results using large doses of Neo-Antergan. In fact, symptoms occurred with greater frequency in the treated group than in controls. Five of 17 patients receiving Neo-Antergan developed a rash between the shoulder blades which persisted as long as the drug was given. This type of reaction has not been reported unrelated to irradiation. Mains (375) reduced the incidence of skin reactions of radiation sickness, such

64 per cent, while Thephorin was effective in 28 per cent. Pyribenzamine, Histadyl, Antistine and several unmarketed compounds gave poor results. Berger (31) found Thephorin of value in 13 of 24 patients.

The mechanism of action of these agents in parkinsonism is unknown, although the effect probably can be explained by the sedative, atropine-like antispasmodic action to be found in drugs such as Benadryl. In the report of Naide (404) on the use of Benadryl in the treatment of nocturnal leg cramps, the good results in all 17 cases treated can probably be similarly explained.

A patient with myotonia atrophica treated by Bussell (70) with Benadryl and later with Neo-Antergan obtained striking improvement. A patient with trigeminal neuralgia, whose attacks could be provoked by the injection of histamine, was relieved by Pyribenzamine and Benadryl. Horton and Brennan (276) believed that this case possibly had an allergic basis. Multiple sclerosis was not helped by these drugs in one series (198)

The results of the use of antihistaminic agents in the treatment of migraine have been equivocal. Most reports deal with only a few cases. Six of 20 patients with migraine treated with Phenergan by Halpern and Hamburger (254) were improved. Eight of 12 patients treated with Thephorin by Cohen *et al.* (95) had 50 per cent or more relief. The report of the Committee on Therapy of the American Academy of Allergy (98) on Trimeton dealt with 44 cases, in 20, good or excellent results were obtained. Four patients with migraine treated with Thephorin by Reynolds and Horton (442) had no relief, and of nine with histamine cephalgia only

Neo-Antergan with similar results. However, as in other conditions, not all patients were relieved.

OTHER CONDITIONS

We, as well as others, observed that Pyribenzamine ointment would prevent the erythema of sunburn. At first it was thought that the effect was related to histamine release; however, it was observed by Kline and Baer (310) that this erythema could also be prevented by placing the Pyribenzamine in quartz cups between the skin and the light source. In other words, Pyribenzamine acts as a filter to the erythema-producing ultraviolet rays of sunlight. Benadryl did not give as good results. Friedlaender, Friedlaender and Vandenbelt (203) also observed this effect. Pyribenzamine, Thenylene, Neo-Antergan, Pyrrolazote, Tagathen, Neohetramine and Antistine had an absorbing effect, while Benadryl, Decapryn, Trimeton and Thephorin did not. Others (472) have found that para-aminobenzoic acid is highly effective, and we have observed that it is better than Pyribenzamine.

The symptoms of experimentally induced frostbite were alleviated by pretreatment with Benadryl and Pyribenzamine applied by iontophoresis. Macht *et al.* (369) believed that histamine or a histamine-like substance is liberated in the human skin in the early stages of frostbite.

Alteration in the course of infectious processes has not been demonstrated in man, but Halpern (251) noted that animals injected with large amounts of antihistamines had septic infections from localized lesions

rated these conditions in most of the cases. To our knowledge this has not been confirmed.

Sensitivity to sunlight (544) and to cold (408, 412) has been treated with these compounds, with variable results. Improvement in capillary resistance following use of the antihistamines has been reported by some investigators (258, 477a), while others have noted no changes in the permeability of the meningeal capillaries (224). Adlersberg (8) suggested use of these drugs in the treatment of gout caused by allergy. He mentioned no cases on which this opinion was based. Moseley (400) and Reynolds, Kahn and Levy (441) have used these agents as topical anesthetics. The latter authors found that 1 per cent solutions of Pyribenzamine, Neo-Antergan and Benadryl produced anesthesia in all but one of 45 patients in 15 minutes, that this effect lasted about one hour and that no toxic effects were found.

Finally, the commonest side effect of these drugs, sedation, can be utilized to advantage. We have administered drugs such as Phenergan, Benadryl and Decapryn on occasion to patients for this sedating action, especially when barbiturates are not tolerated.

CHAPTER 9

Administration and Dosage

IN THIS CHAPTER we shall discuss the methods of administration of the antihistamines, the dosage of the various drugs and the conditions influencing dosage, the combination of drugs, the choice of an antihistamine and similar details relating to therapy.

Conditions Determining Size of Dose

From the concept of the mechanism of action of the antihistamines it would be expected that in conditions of the same type and severity all persons would respond equally to the same dose of drug. Clinical observation fails to agree with such expected results. Of two persons with vasomotor rhinitis or urticaria of moderate grade, one may require doses of 25 mg. for relief and the other may need 100 mg or more. In fact, in the one case the drug may work in small doses and in the other it may be ineffective in any amount. The basis for this individual response is not known, although one or two possibilities might be visualized One might be dealing with individual differences in degradation or enzymatic de-

struction of the antihistamine. Another possibility is that even though allergic symptoms are of equal intensity in both cases, the amount of histamine required to produce them may be much greater in the second case because of a smaller responsiveness of the tissues. In addition to this basic individual difference, there appears to be periodic fluctuation in responsiveness in any one person for which no cause can be assigned. What has been said about therapeutic response also applies to differences in the capacity to tolerate these drugs.

Perhaps the factor which most influences the size of the dose of an antihistamine is the severity of the symptom. A slight urticarial rash may be completely relieved by 25 mg doses of most of the antihistamines, but relief of severe urticaria and angioneurotic edema may require 150–200 mg doses of the same drugs. On many occasions we have been called in to see patients who had a severe "serum type" of reaction following penicillin or sulfonamide therapy and who were regarded as having failed to respond to antihistamines. Merely changing the dose from 50 to 100 or 150 mg. was sufficient in most instances to produce a prompt effect. This experience is shared by others. For example, Peterson and Bishop (426), in treating serum sickness in children with Benadryl, found that 50 mg doses were not always effective whereas 100 mg doses produced results in all patients.

Gastrointestinal absorption of the drugs may differ not only *among individuals* but also in the same person on different occasions An empty stomach will absorb the drug more quickly than a full one, and thus the actual blood titer will be higher. Not infrequently about one-

half the dose, if given before meals, will produce the same effect as a full dose. The drug might be prescribed before or after meals depending on the rapidity and extent of effect desired, but whatever the method, it should be followed consistently in the same patient. It might be added that there is less tendency for gastric irritation to occur when the drug is taken on a full stomach Gastrointestinal disturbances, such as pylorospasm, nausea, infectious disease and conditions of generalized edema, may also influence absorption and thus modify the effective dose. It is even possible that a large dose of an antihistamine which produces considerable nausea may modify gastric absorption to an extent that the dose is therapeutically less effective than a smaller dose which does not produce this gastric change. This result was supported by our experience (75) in studying the effect of various doses of antihistamine on the degree of inhibition of the histamine flare.

The size and age of the individual have a definite relation to the size of the dose. Large persons usually require larger doses. Older persons require about the same doses as younger persons but usually do not tolerate them as well. Children require smaller doses, although moderate doses are usually tolerated better by them than by adults. Although there are many variations and individualities, we have observed the following general rule for dosage in children. Those over 12 or 14 years of age are given adult doses. Children over 5 and up to 10 or 12 years are given 50 per cent of the adult dose and those from 2 to 5, 33 per cent. In infants 2 years or under doses vary from 5 to 25 per cent of the adult size.

With any particular drug or any individual patient the size of the dose must be considered in terms of the therapeutic/toxicity ratio. A drug which in 25 mg. doses normally causes some sedation or sedates a particular patient cannot usually be used in doses higher than 50 mg. A drug which in usual doses may produce little or no sedation but also little therapeutic effect may still not have an advantage over others, because at effective levels the toxicity may be as great or greater than that of other drugs

The patient's activities and duties often determine the size of the dose, mainly because of the factor of tolerance It is usually feasible to give larger doses when the person is at home and even larger doses when he is in bed, because sedation and objections to loss of alertness and diminished power of concentration are less of a consideration Those who must use maximal powers of mental concentration or must be completely alert, such as students and other professional and business people, must confine themselves to smaller doses of antihistamines Even those who do physical work may have to have the dose of drug reduced if it causes lassitude or muscular weakness. For aviation pilots, trainmen and those in other critical occupations, the use of any amount of the antihistamines while on duty is questionable.

Dosage of Individual Drugs

The doses of the antihistamines not only vary with the factors just discussed and with the physician's custom, but may vary strikingly depending on the individual drug The differences in individual compounds are

predicated both on the degree of effectiveness and limitations due to toxicity. Despite the claim of many manufacturers that their compound is the most potent or the least toxic, generally speaking, these two phases neutralize each other. Usually the most potent drugs are also more toxic; thus, although milligram potency may be greater, the higher toxicity will as a rule prevent the use of a dose as large as that of a less toxic drug. An extremely potent antihistamine with a very low toxicity, resulting in a very high potency/toxicity index, has not yet been presented and perhaps never will be.

TABLE 2.—DOSES OF ANTIHISTAMINES (IN MILLIGRAMS) FOR ADULTS

	AVERAGE DOSE	MINIMUM EFFECTIVE DOSE	MAXIMUM DOSES IN SEVERE MANIFESTATIONS
Antistine	100–200	50	200
Benadryl	50	25	200
Chlorcyclizine (Perazil, Di-Paralene)	50–100	25	200
Chlorothen (Tagathen)	50	25	100
Chlor-Trimeton	4	2	12
Decapryn	25	12.5	75
Diatrin	25–50	—	—
Histadyl (Thenylene)	50–100	25	200
Hydryllin	2 tablets	1 tablet	4 tablets
Neo-Antergan	50–100	25	200
Neohetramine	100–200	50	200
Phenergan	25	10	60
Pyribenzamine	50	25	200
Pyrrolazote	50	25	100
Thephorin	25–50	25	100
Trimeton	25	12.5	100
p-Fluorobenzyl-DPE (Lederle)	30	15	50–75
194B (White)	50	25	200

The following brief discussion of doses of the various

antihistamines is based in large part on our experience and also on the experience of others.

Antistine.—The average doses are 100–200 mg. Even in these doses this drug is not highly effective. Most clinical investigators have employed 100 mg. doses. We feel that for results comparable to those obtained with potent drugs much larger doses would have to be given, but we are not sure whether this could be done safely. In moderate doses the drug is only mildly sedative.

Benadryl.—A dose of 50 mg. is average, and the usual range is 25–100 mg Under special conditions much larger doses have been given. This antihistamine is effective in the majority of cases in which antihistamines work. Its chief disadvantage is the tendency to cause sedation, at times, however, this effect is advantageous

Chlorcyclizine.—Our average doses have been 50 and 100 mg We have also used 200 mg. on occasion. Good results from 25 mg doses have been claimed, but the Committee on Therapy of the American Academy of Allergy (99) found that a dose of 50 mg two or three times daily is required for effective results The sedative action is mild.

Chlorothen.—The average dose of this drug is 50 mg. The usual range is 25–100 mg. We have rarely used larger doses Sedation is moderate.

Chlor-Trimeton.—The average dose in our experience is 4 mg Doses of 8–12 mg. are not well tolerated. Eisenstadt (149) used doses of 2–4 mg., and the Committee on Therapy of the American Academy of Allergy (99) also obtained good results with 2–4 mg.

antihistamine, 200 mg. of Neohetramine would probably be required. Sedation from moderate dosage is slight.

Perazil.—See chlorcyclizine.

Phenergan.—This drug is marketed in Europe. It has also been used in our laboratory and in clinical trial by us and others in this country. The average dose we have used is 25 mg. In some cases, particularly when the drug was administered in the evening, 50–60 mg. was given. Doses of 10 or 15 mg. can also be effective. This is the most sedative of all the antihistamines.

Pyribenzamine.—The average dose is 50 mg., and the usual range is 25–100 mg. In severe manifestations we have used doses of 200 mg., but with such amounts the patient must be under close observation. Sedation is moderate.

Pyrrolazote.—A 50 mg. dose is average. Much smaller doses are not very effective and much larger doses are not well tolerated. In average dosage this drug is moderately sedative.

Tagathen.—See chlorothen.

Thenylene.—See Histadyl.

Thephorin.—The average dose is 25 mg. Doses of 50 mg. produce a high incidence of gastric upsets and excitatory phenomena. The incidence of sedation is low, but stimulation is common.

Trimeton.—A 25 mg. dose is most common. Doses of 50 mg. have been used, but with these and larger doses a high frequency of sedation is encountered. Good results have also been claimed with 12.5 mg. doses (63).

p-Fluorobenzyl-DPE (Lederle).—Since this drug has

or capsule in the morning may be all that is needed. In other patients night symptoms may best be modified by a bedtime dose. In some patients we have found that a bedtime dose, by improving the nasal congestion at night, benefits the morning symptoms.

Whether the dose is taken regularly or is taken in the morning and at bedtime, it is often of advantage to take different types of antihistamines in the daytime and in the evening The less sedative varieties, such as chlorothen, Pyribenzamine, Thenylene and Thephorin, may be used in the daytime; the more sedative ones, such as Benadryl and Decapryn, may be more desirable at night.

Two drugs in particular are likely to produce an effect longer than average in duration. These are Di-Paralene (Perazil) and Phenergan. The effect may last for a period of eight to 12 hours with moderate doses, perhaps longer with larger doses

Several objective studies have been made which corroborate the clinical observations of duration of action of the antihistamines McGavack and associates (364) studied the blood levels of subjects who were given 400 mg of Benadryl or Pyribenzamine. Peak values were found at 90–120 minutes Since the dosage was unusually large and severe gastric symptoms were produced, these findings cannot be taken as representative. Perry and Heatin (424) determined the threshold whealing response to histamine by iontophoresis. They found that after 50 mg of Benadryl or Pyribenzamine or 2 tablets of Hydryllin the maximal inhibition was at two hours and the total duration of measurable effect

acquainted with the characteristics and peculiarities of a score of antihistaminic drugs.

For practical purposes and for most occasions we would advise that the average physician become conversant with one member of each of three groups The groups may be divided as follows: Group 1 comprises the less sedative and usually less potent drugs and in it may be included Antistine, Neohetramine, Thephorin and chlorcyclizine (Di-Paralene, Perazil). Group 2 contains the potent and moderately sedative varieties and includes chlorothen, Chlor-Trimeton, Diatrin, Histadyl (Thenylene), Neo-Antergan, Pyribenzamine, Pyrrolazote and Trimeton. Group 3 comprises potent, highly sedative drugs and contains Benadryl, Decapryn and Phenergan. If the practitioner will adopt one of each group for his armamentarium, the trio selected should provide an effective range for most needs For example, he might choose the trio of chlorcyclizine, Pyribenzamine and Decapryn. If the patient becomes sedated from Pyribenzamine, it is obvious that chlorcyclizine rather than Decapryn would be tried next On the other hand, if a greater sedative action is desired Decapryn would be chosen. The patient's temperament and his past behavior to other antihistamines often give a clue to the variety to try Another combination, for example, would be Thephorin, Thenylene and Benadryl.

The choice of a particular drug is also influenced by specific needs For instance, at night and particularly in itching conditions a highly sedative drug may be advantageous. This selection may also apply to a highly nervous person For night, too, long-lasting effects may be

because of the frequent objections to side actions, many drugs have been used with the antihistamines, either separately or in a combination capsule or tablet. One of the most common objectives in therapy is to neutralize the sedative action of the antihistamines by the use of stimulants It should be emphasized at the outset that to accomplish this is not as simple as it sounds. It is not easy to judge the amount of stimulant required; if too much is given there is overstimulation, if not enough, sedation is still present. Furthermore, the duration of the effect of each (stimulation and sedation) is not necessarily the same. Here again the relative doses for the individual must be juggled, and it becomes obvious that a predetermined combination in a manufactured tablet is more apt to be unsuitable than suitable for any particular case. The medication must be in a form amenable to change in proportions. The principal drugs which have been used are amphetamine, ephedrine, aminophylline and caffeine. Amphetamine, desoxyephedrine and related drugs are probably the best for this purpose, when no action other than stimulation is desired.

On rare occasions, the addition of a sedative is advantageous when the excitatory action of a particular antihistamine is objectionable.

In some instances benefit may be gained by combining two antihistamines The purpose may be an attempt to administer a higher total dose by using a stimulating with a sedating antihistamine. For example, one might combine Benadryl with Thephorin. Or, if Pyribenzamine happens to be stimulating in the particular patient, the

offered in tablet form, including Thenylene with ephedrine, Pyribenzamine with ephedrine, etc. (see Appendix).

Analgesics have also been combined with antihistamines, primarily for the treatment of colds. Aspirin, acetophenetidin and caffeine are the most common. Therapy of colds with antihistamines has been discussed in a previous chapter. Attention should be called to the possible hazards of prescribing combinations containing aspirin or other analgesics to which allergic persons are often highly sensitive

Method of Administration

Oral—The most commonly used route of administration of antihistamines is the oral one. In most instances this route of medication is effective and adequate. Disadvantages include the objectionable taste of the drug and the fact that under certain conditions absorption from the gastrointestinal tract is poor or uncertain.

For oral use the drug is usually procurable in capsules or pills which are sugar coated, in plain compressed tablets or in grooved tablets The form of the unit may appear offhand to be an insignificant factor in therapy, but it is enlightening to see how much more frequently children and even adults will choose a sugar-coated, elegant-looking pill in preference to an equally (or more) effective, soft and bitter-tasting tablet. The number of milligrams contained in each unit dose (capsule or tablet) is of considerable practical importance. For example, if the average effective dose is 50 mg and the drug comes in 25 mg tablets, the incidence of effectiveness will not be as high as the drug deserves. It is an

almost universal reaction for the patient to regard two tablets as a double dose. If he takes two he regards himself as heroic, and rarely will he take more. If the 50 mg. is placed in one tablet he still regards it as one dose. We would recommend to the physician that whenever possible he prescribe the intended average dose which comes in one tablet, using a half tablet or a smaller tablet for a smaller dose and two or more regular-sized tablets for a larger dose. We would further recommend to the manufacturers that such an arrangement of units would be to the best advantage for effectiveness of their product.

Enteric coating has been used by several pharmaceutical houses to produce delayed antihistamine effect. The products are primarily for use at night when action is desired several hours later. If symptoms are present at bedtime a plain tablet or capsule should, of course, be taken together with the enteric-coated one. One manufacturer has combined the two features in one tablet, with the immediately dissolved antihistamine on the outside and the enteric-coated dose in the core of the pill. Theoretically, the enteric coating would frequently be considered highly desirable were it not for the fact that the behavior of such coatings is notoriously uncertain.

Elixirs or sirups of most of the antihistamines are obtainable. The amounts vary for different antihistamines, but for most the dose per teaspoonful is from 20 to 40 per cent of the average adult dose The chief advantages are, of course, that use of this form is practical for children and that the dose can be made more elastic.

Injection.—Intramuscular or intravenous administration of antihistamines is useful at times. These methods are certainly not indicated for routine use or in ordinary cases. Now and then there may be reason to suspect that gastrointestinal absorption is poor or unreliable, and injection of the drug may change a poor result into a good one. Injection may also be indicated when rapid effect is desired, as in allergic emergencies such as allergic reactions to injections or edema of the larynx. In such cases, it should be remembered that epinephrine and not an antihistamine is the first drug to be used, to be followed by the antihistamine if desired. We have used intramuscular injections of Benadryl in patients with dermographism for its quick effect on calming of skin irritability to enable us to proceed with skin testing.

In giving intramuscular or intravenous injections special care is necessary with regard to dosage. Intramuscular or intravenous doses have been 10–50 mg Intravenous injections must be given slowly and the dose should be well diluted Larger doses have been used experimentally by others. Mackmull (371) gave intravenous injections to 55 nonallergic subjects, using Benadryl in doses of 50–300 mg Doses of 100 mg or more always caused reactions, some of which affected the nervous and cardiovascular systems McElin and Horton (362) treated allergic patients with Benadryl, giving 20 mg. intramuscularly or 10–100 mg. intravenously by continuous drip method within a 10 minute period. Side effects are expected with intravenous medication. Rosenberg and Blumenthal (463) reported their results with intravenous use of Benadryl, the average dose being 30

acute attacks were relieved in eight to 10 minutes. Rubitsky *et al.* (473) also described relief obtained with aerosols of Benadryl.

Iontophoresis.—Aaron (1) introduced Pyribenzamine by iontophoresis nasally in five patients with seasonal hay fever, with relief lasting one to four days. Cortés and Rodriguez Herrera (100), however, obtained only brief improvement by nasal iontophoresis of Benadryl. In pruriginous dermatitis their results with this method were similar. Aaron and co-workers (3) obtained good results in dermatitis associated with pruritus by iontophoresis of 5–10 per cent Pyribenzamine.

Topical applications to skin.—Following extensive experimentation with topical applications of antihistamines to the skin, we (181) reported in 1947 that an ointment of 2 per cent Pyribenzamine was effective in a number of pruritic conditions, including atopic dermatitis and pruritus ani. Since then a number of pharmaceutical houses have put out antihistamine ointments and creams, using various bases. Topical applications are helpful, particularly if the lesions are not too widespread. They should not be used on acutely inflamed skin. Some skins are irritated by the ointments, while others develop a contact dermatitis The preparations we have used most frequently are Pyribenzamine cream and Thephorin ointment. When a more greasy protective covering is desired Pyribenzamine ointment should be used. On a few occasions we have found a solution preferable to an ointment.

Pyribenzamine cream was found effective in lichen simplex chronicus by Sulzberger *et al.* (530). In atopic

dermatitis they found it ineffective. Laymon and Schmid (324), D'Avanzo (121) and Woolridge and Joseph (582) reported on the use of Thephorin ointment in various dermatoses. Strauss (525) used it in bee stings On the other hand, Perry (422), using Benadryl ointment, and Peck and associates (417), using Pyribenzamine ointment, found little effect on the histamine wheal and flare.

CHAPTER 10

Toxic Effects

IN THIS CHAPTER we shall discuss primarily the undesirable actions of the antihistamines. However, it may be fitting at this point to reiterate briefly the limitations of the therapeutic actions of these drugs, which constitute undesirable features in themselves

The antihistamines do not influence all histamine effects. For example, the histamine stimulation of gastric secretion is not affected by these drugs There is evidence that in addition to histamine release there are other mechanisms in anaphylaxis and allergy, and these are not modified by the antihistaminic compounds Even though a type of allergic manifestation may owe its major symptoms to histamine, in some particular individuals, for reasons unknown at present, the antihistamines may be ineffective There are also degrees and stages of any allergic syndrome which may fail to respond to these drugs The net result is that the action of these compounds is at best virtually never complete There is also the obvious limitation in usefulness resulting from the palliative nature and the short-lasting action of these

with undesirable or toxic effects. Since the entire series of antihistamines have much in common in this phase of their activity, we shall discuss the various untoward reactions as a group and later make a few remarks about each drug

Sedation—The sedative effect of the antihistamines is their most characteristic side action. Depending on the individual susceptibilities of the person, the nature of the specific drug and the dose, this sedative action may assume varying degrees of severity The mildest effect is one of calming the patient, making him less taut or nervous than he is normally. If this influence does not progress to a more intense action, the result may be desirable The next stage is one of diminishing alertness or slight difficulty in mental concentration. The patient may feel somewhat detached from his environment and is less responsive to outside stimuli He may feel as if he is "walking on air." There may be a feeling of numbness This stage may proceed to a stage of confusion and even to disorientation.

In more severe effects the patient becomes groggy and, if still more severe, very sleepy. The sedative effect often reaches a stage comparable to that obtained from a soporific dose of a barbiturate and not infrequently the effect is even more pronounced The hypnotic effect is useful at times, if the patient takes the drug at night or if he is confined to his home in the daytime For the most part, however, this sedative action, except in its mildest form, is objectionable and endangers the patient as well as those who are dependent for their safety on his alertness Sedation of one degree or another is a common ef-

fect of the antihistamines, the incidence varying from about 20 to 60 per cent with average therapeutic doses. There is a tendency to develop tolerance for the sedative action, sometimes after the first few doses of the drug.

Excitation.—In very large doses excitation will occur with all antihistamines, the ultimate effect being exhibited in the form of convulsions. With average clinical doses of most antihistamines, excitatory phenomena occur in a minority of patients Certain individuals are more apt to respond by stimulation than by sedation. This is particularly true of highly nervous persons and of young children. Excitatory phenomena are more common in children than in adults. In this respect children approach more closely the toxicity pattern observed in experimental laboratory animals in which excitatory phenomena from these drugs are the rule

In its mildest form, stimulation may be confined to a feeling of increased energy and well being and greater talkativeness The effect is seldom confined to this stage, however, but proceeds usually to more objectionable features. A feeling of nervousness or jitteriness is most common Dizziness and unsteadiness of gait may occur, although these effects are probably more often produced by sedation Shaking and muscular tremors may constitute a severer form of excitation Muscle twitching and delirium are signs of more advanced stages of cerebral stimulation and should be regarded as a danger signal Convulsions will, of course, take place in the severest forms of excitation. It is noteworthy that when fatal poisoning from antihistamines has occurred convulsions have appeared to be a characteristic manifestation

Other neuromuscular effects noted and not always classifiable are headaches, blurring of vision and other visual disturbances, faintness and muscular weakness.

Digestive tract.—Symptoms referable to the digestive tract are not uncommon. Although some of the antihistamines are more likely to produce gastrointestinal irritation than others, all are capable of doing so The source of such upsets is of two types, systemic or toxic and chemical, by direct irritation of the mucosa. Perhaps the commonest symptom produced is epigastric distress, often associated with pyrosis. Nausea not infrequently occurs and, in severe cases, vomiting may follow. Intestinal symptoms, such as colicky pain, distention and diarrhea or constipation, may also be part of the digestive tract disturbance The antihistamines tend to produce gastrointestinal symptoms in persons who have other gastrointestinal abnormalities, such as peptic ulcer or irritable colon

Dryness—An atropine-like action on the salivary and nasal secretions is not rare In mild forms it is usually not noticeable, particularly when diminution of excessive secretions, as in vasomotor rhinitis, is beneficial However, it often happens that the drying effect is excessive and objectionable The extreme dryness of the nose and throat may be worse than the rhinorrhea of the disease. Dryness of the mouth, due primarily to an effect on the salivary glands, may be a valid reason for discontinuing use of the drug The gland-inhibiting action may extend to the mucous glands of the bronchi and produce a diminution in expectoration which sometimes results in aggravation of the asthma.

Cardiovascular system.—The effects on the cardiovascular system are chiefly those of excitation. Palpitation and tachycardia are perhaps the commonest complaints in this group. Frequently these symptoms are accompanied by a fall in blood pressure, although hypertension from antihistamines is observed at times. Precordial discomfort and arrhythmia have also been noted.

Other side actions.—Difficulty in urination, particularly in men with enlarged prostates, occurs at times. Occasionally this may result in complete urinary obstruction (581). Sometimes urinary frequency is a symptom. Diminution in libido has been noted, an effect which is probably secondary to a sedative action. Various types of skin lesions have been described

Toxicity Features of Individual Drugs

In discussing the variations in kind and degree of side actions of the different drugs we are moved to point out again that such data and opinions are beset with many pitfalls. Even though we have had opportunity to compare almost all the antihistamines under reasonably similar conditions and frequently in the same patients, we feel unable to give conclusive opinions concerning moderate differences between various antihistamines In most instances we can only point out impressions, although we have available figures for toxicity observations for most of these drugs

Antistine.—Arbesman (15) made a comparative study of the clinical toxicity of five antihistamines In some of the patients all the drugs were compared. Antistine caused side effects in 14 per cent of patients,

whereas Neohetramine showed a 16 per cent incidence, Pyribenzamine 26 per cent, Neo-Antergan 33 per cent and Hydryllin 35 per cent. Schwartz (481) in a similar study found the incidence to be 23 per cent for Antistine, 7 per cent for Neohetramine, 20 per cent for Histadyl (Thenylene), 25 per cent for Neo-Antergan, 35 per cent for Pyribenzamine and 61 per cent for Benadryl. Overton (414) found side actions with Antistine in 16 per cent of patients and reported that one child had convulsions from a 100 mg. tablet. Our experience and that of the vast majority of other workers indicate that in moderate doses Antistine is one of the least toxic of the antihistamines. It bears repetition that, in the doses discussed, this drug is also one of the least effective, and it is probable that with doses large enough to approximate therapeutic effects of more potent drugs this compound may have no advantage on a toxicity basis. The side actions are the usual ones, described earlier.

Benadryl—This antihistamine belongs to the highly sedative class We have found an incidence of sedation of about 50 per cent with 50 mg. doses. Excitatory effects are not as common as they are with some of the other drugs, unless very large doses are used, nor are gastric irritations as likely to occur with Benadryl as with some of the other less sedative drugs. Levin (334) reported a 60 per cent incidence of sedation and noted that the development of tolerance to sedation was common He also reported other side actions, such as weakness, stupor, narcolepsy and confusion. Waldbott (555) claimed that most of his patients taking Benadryl had some degree of dizziness and sleepiness. Two com-

plained of muscular twitching and in three asthma was aggravated. Loveless and Brown (359) noted a 60 per cent incidence of sedation, while Waldriff and co-workers (557) reported this effect in 43 per cent of patients, compared to 25 per cent with Thephorin, 24 per cent with Trimeton, 23 per cent with Histadyl, 22 per cent with chlorothen, 20 per cent with Neo-Antergan and 19 per cent with Pyribenzamine.

Chlorcyclizine (Di-Paralene, Perazil).—The toxicity index of this drug is low and its side actions usually mild. With 50–100 mg. doses we (179) found the incidence of side effects to be 18 per cent. Sedation was the commonest effect. Diarrhea, cardiac symptoms, headache and excessive dryness were noted occasionally. Moderate to severe side effects were observed in 12.6 per cent of patients by members of the Committee on Therapy of the American Academy of Allergy (99), whereas Jaros and associates (289) noted a 33 per cent incidence of side effects in 30 subjects who were given doses of 100 mg.

Chlorothen (Tagathen).—The toxic effects from this antihistamine are about the same as those of most other drugs of this class. The major effect is sedation, although other effects noted were nausea and indigestion. Occasionally, headache, constipation or an itching rash occurred. In a series of 232 patients we (176) found an incidence of side effects of 30 per cent In a small series of cases, Taub and his associates (535) noted an incidence of 10 per cent. However, the size of the group is too small to be statistically significant

Chlor-Trimeton.—Moderate to severe side effects were observed in 7.5 per cent of a large group of pa-

tients who received doses of 2–4 mg. (99). The percentage of those having mild toxic reactions was not recorded in this report. Many of our patients have required larger doses (4–12 mg) to obtain good therapeutic effects, and with these doses the side actions are considerably more frequent and severe.

Decapryn.—This drug, in average therapeutic doses, is one of the most sedative. In doses of 12.5 and 25 mg, more often the latter, we (183) found an incidence of side actions of 34 per cent. Most effects were variations of sedation, although headache, epigastric pain and dermatitis were occasionally noted. Although the incidence of side actions with these doses is probably lower than that for Benadryl, larger doses of Decapryn, say 50–75 mg, produce more frequent and more severe reactions than 50–100 mg doses of Benadryl Sheldon and co-workers (499) reported drowsiness in 57 per cent of patients Brown and his associates (65), on the other hand, claimed that side effects were produced in less than 10 per cent of those taking doses of from 12 5 to 50 mg

Diatrin.—In a study of a series of patients with dermatoses, Combes and his co-workers (97) reported a 21 per cent incidence of side effects, most of which were gastrointestinal

Dramamine.—This compound is used especially for motion sickness As is the case with Benadryl, Simon and Seyler (505) noted considerable drowsiness from Dramamine and warned against its use in pilots

Histadyl (Thenylene).—In average therapeutic doses we (182) have found the drug to be moderately seda-

tive. The incidence of side effects, most of which were forms of sedation, was 25 per cent. Other unpleasant symptoms noted at times were vertigo, dryness of the mouth and throat, excitation, insomnia, headache, nausea and diarrhea. Friedlaender and Friedlaender (202) also observed side effects in 25 per cent of patients, and Schwartz (481) in 20 per cent. Peirce and Mothersill (418) stated that side effects were infrequent.

Hydryllin.—This is a combination of diphenhydramine and aminophylline. The side effects in general are of three types. The Benadryl is responsible for the sedation. This side action has not been drastically reduced if a dose of 2 tablets (which equals 50 mg. of Benadryl) is used. A few patients note the excitatory effects of the aminophylline, while others have gastrointestinal irritation, also primarily due to the aminophylline. Arbesman (15) noted a 35 per cent incidence of side effects, Markow and his co-workers (380) a 37 per cent incidence, and Levin and Moss (335) a 25 per cent incidence. Levin and Moss remarked that the 25 per cent figure compares favorably with the frequency of side effects when Benadryl alone is used. However, they used only 1 tablet of Hydryllin, which is equivalent to 25 mg. of Benadryl.

Neo-Antergan.—This drug belongs to the group with a moderate incidence and degree of side effects. In 50 mg. doses it is probably less sedative than Pyribenzamine. However, 100 mg. doses are often required for moderately severe allergic conditions. Neo-Antergan has a rather common tendency to produce gastrointestinal symptoms. Arbesman (15) found a 33 per cent in-

cidence of side effects from this drug, and Schwartz (481) noted a 24 per cent incidence.

Neobetramine.—This is unquestionably one of the least toxic of the antihistamines when used in doses of 50–100 mg However, in such doses the efficacy of this drug is poor. Much larger doses have not been consistently employed in therapy, but if such large doses were used, the toxicity would probably be as great as that of the more toxic drugs. The commonest side action is sedation. With doses of 50 mg. we (32) obtained an incidence of side actions of 9 per cent, with 100 mg., 16 per cent. Arbesman (15) noted an incidence of 16 per cent, while Criep and Aaron (108) reported 10 per cent, and the Friedlaenders (207) gave an incidence of 12 per cent for doses of 50–100 mg.

Pyribenzamine.—This antihistamine is in the group having moderate side effects. Its major side action is sedation, although in a fair number of persons excitatory phenomena may result. Gastrointestinal symptoms are not rare Toleration on the whole is about on a par with that of most of the antihistaminic drugs We (186) found that side effects occurred in 25 per cent of patients, Arbesman (15) noted an incidence of 26 per cent and Schwartz (481), of 35 per cent. Loveless and Brown (359) noted that gastrointestinal symptoms occurred more frequently from Pyribenzamine than from Benadryl

Pyrrolazote—This drug belongs to the moderately toxic group when used in 50 mg. doses In doses of 100 mg or more the incidence and degree of side effects are high Sedation is the commonest toxic action, although



the least toxic of the antihistamines, comparable to Antistine and Neohetramine, but having the advantage of more decisive therapeutic effectiveness. In a series of 249 patients (33), most of whom received 50 mg. doses though many received 100 mg, the incidence of side actions was 16 per cent. Mild sedation was the commonest effect, though a few patients complained of nervousness, gastrointestinal upsets or dermatitis.

p-Fluorobenzyl-DPE (Lederle)—With doses of 30–50 mg (the usual range) the side effects, in incidence and degree, are much like those with average doses of Pyribenzamine In a fairly large series of patients we (178) observed a 19 per cent incidence of side effects.

Severe or Unusual Effects and Special Studies

In this section we shall discuss reports of some of the severe or unusual reactions to the antihistamines, which are usually caused by large doses or prolonged use. However, because of individual susceptibilities, some of these effects have been observed immediately and after use of moderate doses Special studies on toxic effects of these drugs will also be considered.

Nervous system.—Effects on the nervous system are common with large doses and the few mentioned here represent only a small fraction of the incidence Disorientation, confusion and delirium are not infrequent toxic results Borman (45) reported that a nun took 2,000 mg. of Benadryl in 48 hours, with resultant disorientation, confusion and lethargy and with complete recovery 48 hours after discontinuing the drug. The

after a dose of 50 mg. of Benadryl that he wrecked an electric platform cargo truck which he was operating.

Churchill and Gammon (85) studied the influence of Pyribenzamine and Benadryl in epileptics and concluded that both drugs are capable of inducing seizures in persons with focal lesions. Although Pyribenzamine increased the petit mal attacks, Benadryl decreased their frequency. The authors concluded that the antihistamines must be used with care in patients with convulsive disorders.

After moderate doses of Benadryl, acute labyrinthitis occurred in a young man on three occasions (533). Ross (466) reported four patients who had striking ocular changes after taking Pyribenzamine. After daily doses of 75–100 mg for periods varying from two days to one month, three patients noted symptoms of blurred vision, two had refractive changes and one, diffuse corneal edema.

Circulatory and hemopoietic systems.—Since there are frequent clinical reminders that the antihistamines have an excitatory action on the heart, Mackmull (371) studied the effect of intravenously administered Benadryl in normal subjects. The doses used were 50–300 mg., and the commonest reaction was dizziness, which was always present after doses of 100 mg. or more. Tingling, sleepiness and thick speech were common with high doses The systolic and diastolic blood pressures were moderately elevated for about an hour, and the heart rate was increased. With 200 or 300 mg, electrocardiographic changes of significance were present. The author concluded that fairly large doses of Benadryl

counts also showed granulocytic depression. Three cases of hemolytic anemia, reported by Crumbley (110a), were diagnosed 10, 14 and two months, respectively, following frequent, average doses of an antihistamine. In two cases Benadryl was taken and in the third, Pyribenzamine. In all three, the blood picture returned rapidly to normal after discontinuing use of the drug.

Skin.—Rashes from the systemic or topical use of antihistamines occur at times These skin rashes probably comprise two main types, one due to a true allergy and the other to the irritative action of the drug. The second is most apt to occur when the antihistamine is applied topically, particularly when the skin is delicate or highly inflamed and when the nature of the medicament or base is chemically irritating. The allergic type of rash is due principally to topical use of the drugs and is usually a true contact type of sensitization

Two instances of eruptions in patients with atopic dermatitis who were taking Pyribenzamine orally were described by Epstein (156). In one the eruption resembled the eczematoid type and in the other, pityriasis rosea. In both patients the rash cleared after discontinuing the drug and appeared on readministration Rattner and Griffin (435) described a case of dermatitis that appeared on two occasions after the ingestion of a single tablet of Pyribenzamine. Neither Benadryl nor Antistine produced dermatitis in the patient. The authors stated that they had encountered two similar cases Eczematoid dermatitis following the ingestion of Pyribenzamine was reported by Harris and Shure (264) The rash could be reproduced by subsequent administration of the drug

reported by Strauss (524), and by Sulzberger and associates (530) who noted that two of 90 patients treated with topical application of Pyribenzamine developed sensitivity to it.

Thephorin appears to possess an even greater tendency to sensitization. Ellis and Bundick (151) stated that of 50 patients with chronic pruritic dermatoses treated topically with Thephorin ointment or lotion for an average of 50 days, 14 became worse. Patch tests with Thephorin were made on five of the 14 and all gave positive reactions. Reiss and Kern (438) report a 2.5 per cent incidence of contact-type reactions among 120 patients using Thephorin ointment. A sensitivity index of 16 per cent was claimed by D'Avanzo (121).

A case of localized dermatitis from Antistine eye drops was reported by Mosko and Peterson (401). The reaction to a patch test was positive.

Deaths.—The antihistamines are potent drugs, and it has been amply demonstrated that large doses can be fatal. It has been claimed, in addition, that even moderate doses may influence the fatal outcome in some situations. Although only a relatively few fatalities have been recorded in the medical literature, many more deaths suspected to be due to the antihistamines have been described in the newspapers and probably a good many others escape unnoticed. To the cost in lives from these drugs must also be charged all those accidental deaths from automobiles or other machinery used by persons who are in a dopey state from the effects of the drugs. For example, we know of an instance in an Eastern city in which a man, feeling groggy while un-

depression of respiration, cyanosis and high fever developed (122). Unconsciousness followed and the baby died 13 hours after ingestion of the drug. Autopsy findings consisted chiefly of cerebral edema and softening and passive congestion of the liver and kidneys. Tobias (539) described the case of a 21 month old child who swallowed 600 mg. of Anthisan (Neo-Antergan) and lost consciousness within two hours. Profuse catarrhal discharge from the respiratory tract and epileptiform convulsions followed, and death occurred less than three hours after taking the pills. Another instance of death from Neo-Antergan is reported by Deichman (126) in a girl, aged 2, who took 1,300 mg. of the drug, became unconscious, had convulsions and succumbed within 45 minutes.

An editorial (145) in *New York Medicine* warns of the dangers of the antihistaminic drugs to children, particularly when large doses are ingested, and of the hazard of leaving these drugs where children may obtain them. Two fatalities were mentioned. One was that of a 2 year old child who consumed the contents of a bottle containing 19 capsules of an antihistamine (the variety not mentioned). He quickly developed convulsions and became unconscious, his temperature rose to 107.4 F. and he died in 13 hours. Autopsy findings were similar to those found in heat stroke. Another 16 month old infant who took 100 mg of an antihistamine "which is the equivalent of about four tablets generally used for the prevention of the common cold," promptly developed convulsions, followed by a temperature of 107 F., and died in 15 hours.

in *Lancet* stated that "the obvious antidote is histamine acid phosphate, injected subcutaneously in doses of 0.1 mg. per kilogram of bodyweight." The use of large doses of histamine is open to doubt, because it has been shown in guinea pigs that when large doses of antihistamine are used to prevent bronchospasm from large doses of histamine, the animals later develop other histaminic effects such as coma, peptic ulcer, etc. The issue must remain an open one.

Self-Medication—Its Hazards

The present trend of self-medication with the antihistamines, which has become widespread because of permission for over-the-counter sales granted to some of the products by the Food and Drug Administration, has become a real menace to public health. It encourages self-diagnosis and leads to much neglect of proper diagnosis and correct treatment. A "cold," which the sufferer is assured will be completely stopped by the antihistamines, may be not a cold but scarlet fever, virus pneumonitis, sinus infection or other even more serious disease.

The dangers of self-treatment with antihistamines procured over-the-counter are several. Self-treatment results in neglect of proper treatment. It encourages carelessness in the use of these drugs. A large part of the population is not likely to study the fine print of directions on the label, nor heed them if read. Often two or four or a dozen of the tablets are taken, frequently with serious toxic effects. In the ignorant, drug-befuddled or suicide-intentioned person who may take a large num-

taken and similar precautions. Procurement of antihistamines from the pharmacist without permission of a government agency designed to protect the public health has a different connotation from unrestricted over-the-counter sales In the first instance the purchaser knows that he obtains the drug surreptitiously. Knowing that the law requires a prescription, he is inclined to have respect for the potency of the medication and to exhibit greater care in the use and handling of the antihistamine.

The recognized specialists in allergy would be expected to constitute a body of people who have had the most experience with the antihistamines and their toxic properties In preparation for an invited appearance of one of us (S.M.F.) to speak on the subject of the antihistamines before a meeting of the Council on Pharmacy and Chemistry of the American Medical Association a questionnaire was directed to 180 Fellows of the American Academy of Allergy Part of the results of this inquiry has been published (177). The summarized results from 153 replies indicated that about 40 million people were expected to take these drugs. (The actual number is probably much smaller because of counter-publicity by physicians and agencies interested in public health) It was estimated that about 17 million would have mild sedation and eight million, severe. This estimate was based on full therapeutic doses On one-half size doses (the usual dose of over-the-counter drugs) the figures on sedation would be about 10 million Of 144 replies, 131 allergists expressed the opinion that from their experience disregard for label warnings is common with drugs procured over-the-counter. A total

• • • • •

The antihistamines have constituted a valuable advance in the progress of the management of allergic disease and certain other manifestations due to histaminic action. They have been productive of comfort to many sufferers who previously had no ready source of relief These drugs have been of greatest help in seasonal hay fever and of considerable aid also in perennial vasomotor rhinitis In urticaria and angioneurotic edema the antihistamines have proved to be the most effective palliative treatment. In most other pruritic dermatoses they have been of considerable benefit. Used topically, they have also been helpful in difficult dermatitic, nasal and bronchial conditions.

It is essential that proper appreciation be given the fact that these drugs are only of symptomatic benefit, that their activity is of short duration, that they do not help all stages and all varieties of allergy, that they possess toxic potentialities and are highly dangerous if used in excessive doses or if used carelessly or self-prescribed. Many antihistaminic compounds have been marketed—perhaps too many. But the ideal antihistamine has not yet been produced. Such a drug should have all or most of the following characteristics. (1) It should be of very high potency. (2) It should possess a very low toxicity index The important consideration is that the therapeutic/toxicity ratio should be so favorable that, when needed, use of many times the average therapeutic dose should be possible (3) Duration of action should be prolonged. (4) The molecular structure might in-

clude other antiallergic, such as sympathomimetic, actions. Perhaps such an antihistamine is not a possibility. For example, it is conceivable that some of the toxic actions of the antihistamines are dependent on the diversion of the displaced histamine to other tissues.

Even the ideal antihistaminic drug would not comprise the total ultimate goal of solving the histamine problem. There is still room for approaches to the disarming of histaminic action other than by competition. Effective methods of destroying histamine by enzymatic degradation might achieve this end. The prevention of the production of histamine from its precursors—the concept of antihistaminogenesis—is also a possibility.

More recently, experience with ACTH and cortisone has indicated a striking clinical effectiveness in some allergic conditions. It is rather apparent that the mechanism of this action is not based on antihistaminogenesis, histamine competition or histamine destruction. Although the mechanism of action is not definitely known, it is reasonably certain that these hormones produce a chemical or physicochemical alteration in the pathologic tissues to make them less susceptible to histamine effects. The hope of modifying tissue reactivity in general, then, leads to a new approach in the study of treatment of allergic disease.

And finally, there is almost universal agreement that histaminic action is not the sole mechanism involved in atopy and is probably of no importance at all in many other types of hypersensitiveness. In a large group of patients, the management of allergy along allergic lines, including diagnosis, elimination and desensitization,

must not be by-passed or ignored in favor of the antihistamines In addition, progress must continue by research in clinical allergy and by investigations in basic mechanisms involved in etiology and therapy. The concentration of this manual on the subject of the antihistaminic compounds and the omission of a consideration of the general subject of allergy should not be regarded as an indication that these drugs have solved the allergic problem. It happens that this is not a treatise on allergy. This is a book on the antihistamines

(Diphenhydramine 8-chlorotheophyllinate, Dimenhydrinate)		Hydryllin with Racephedrine	Tablet	25 mg. + 100 mg aminophylline + 25 mg. racephedrine HCl
		Hydryllin Compound	Liquid	4 ml. = 6 25 mg. + 25 mg aminophylline + 15 mg potassium iodide + 8 mg. chloroform + 2 8 Gm. sugar, 2.5% alcohol
		Hydryllin Elixir	Liquid	4 ml = 12.5 mg. + 50 mg. aminophylline, 19% alcohol
		Dramamine	Tablet	50 mg.
		Dramamine	Liquid	4 ml = 12 5 mg., 5% alcohol
Chlorcyclizine hydrochloride	Abbott	Di-Paralene	Tablet	25 and 50 mg
	Burroughs Wellcome	Perazil	Tablet	50 mg.
Chlorothen citrate	George A Breon	Ternoxydyne Compound	Tablet	25 mg + 320 mg. acetophenetidin + 32 mg caffeine
	Lederle	Tagathen	Tablet	25 mg.
	Whittier	Chlorothen	Tablet	25 mg
		Caubren Compound	Tablet	25 mg + 320 mg acetophenetidin + 32 mg. caffeine

Diatrin (N,N-dimethyl-N' phenyl-N'-(2-thienylmethyl)-ethylenediamine monohydrochloride)	Wm R Warner	Diatrin	Tablet	50 mg
Dramamine (see Benadryl)				
Histadyl (Thenylpyramine hydrochloride)	Abbott	Thenylene	Tablet	25, 50 and 100 mg.
		Thenylfred	Tablet	50 mg + 25 mg. ephedrine HCl
		Thenylene and Desoxyn	Tablet	50 mg. + 25 mg desoxyephedrine HCl
		Thenylene Cream	Ointment	2%
		Thenylene-APC	Capsule	25 mg + 230 mg aspirin + 150 mg. acetophenetidin + 30 mg. caffeine
	Blue Line Chemical	Methapyrilene hydrochloride	Tablet	50 mg
	Chilcott (Maltine Co)	Pentryl	Tablet	50 mg + 16 mg. ephedrine HCl + 16 mg pentobarbital sodium
		Pentryl	Enteric-coated tablet	50 mg + 16 mg ephedrine HCl + 16 mg. pentobarbital sodium
	Cole Chemical	Histafed	Capsule	25 mg. + 8 mg. ephedrine HCl + 10 mg. ascorbic acid

APPENDIX. PROPRIETARY ANTIHISTAMINIC PREPARATIONS (*Continued*)

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Histadyl (*cont.*)	Eli Lilly	Pulvules Histadyl	Capsule	25, 50 and 100 mg.
		Histadyl	Injectable	20 mg./ml.
		Cream Histadyl	Ointment	2%
		Cream Histadyl-*Surfacaine*	Ointment	2% + 0.5% Surfacaine (cyclomethycaine)
		Enseals Histadyl	Enteric-coated tablet	50 mg.
		Histadyl	Ophthalmic ointment	0.5%
		Pulvules Histadyl-ASA Compound	Tablet	25 mg. + 3½ gr. aspirin + 2½ gr. acetophenetidin + ½ gr. caffeine
		Pulvules Histadyl-Ephedrine HCl	Tablet	25 mg. + 8 mg. ephedrine HCl, 50 mg + 16 mg. ephedrine HCl
		Solution Histadyl	Liquid	0.5%
		Histadyl	Liquid	4 mg./ml.
		Histadyl Compound-Ephedrine and Codeine	*Liquid*	each oz. = 80 mg + 1 gr. codeine + ½ gr. ephedrine

	Histadyl-Surfacaine	Lotion	2% + 0.5% Surfacaine (cyclomethycaine)
	Hista Clopane Pulvules	Capsule	25 mg. + 12.5 mg cyclopentamine
Flint, Eaton	Pyrathyn	Capsule	50 mg.
	Capathyn	Tablet	20 mg. + 230 mg. aspirin + 150 mg. acetophenetidin + 30 mg. caffeine
	Pyracol	Liquid	each oz. = 160 mg. + 778 mg ammonium chloride + 618 mg. citric acid + 130 mg. chloroform + 6 mg. menthol
McNeil	Methoxylene	Tablet	50 mg. + 2.5 mg racemic desoxyephedrine HCl
	Corenil	Tablet	25 mg. + 7.5 mg. extract belladonna + 1.25 mg. racemic desoxyephedrine HCl
S. E. Massengill	Semikon	Tablet	50 mg
	Semikon	Enteric-coated tablet	50 and 100 mg.
	Dasikon	Capsule	25 mg. + 30 mg. caffeine + 200 mg. aspirin + 120 mg. acetophenetidin + 0.06 mg. atropine sulfate

	Dolopar	Tablet	32 mg + 225 mg aspirin + 162 mg acetophenetidin + 15 mg caffeine + 1 minum tinct gelsemium
Otis Clapp	Pyranisamine Maleate	Tablet	25 mg
Columbus	*Pyramal*	Tablet	50 mg
	Pyrasal	Tablet	25 mg + 325 mg. aspirin + 16 mg caffeine
Direct *Sales*	Pyranisamine Maleate	Tablet	25 and 50 *mg*.
Merck	Neo-Antergan	Tablet	25 and 50 mg
Premo	Pyranisamine Maleate	Tablet	50 mg
	Neo Calotan	Tablet	1¼ gr + ½ gr. caffeine + 2½ gr acetophenetidin + 3½ gr. aspirin
Professional *Drug* Service	Neomine	Tablet	25 mg
	Acetomine	Tablet	25 *mg*. + 3½ gr aspirin + 2½ gr. acetophenetidin + ½ gr caffeine
Rexall	Pyranisamine Maleate	Tablet	25 and 50 mg
	Monhiston with APC	Tablet	25 mg + 2½ gr acetophenetidin + 3½ gr aspirin + ½ gr caffeine
William H Rorer	Thylogen	Tablet	25 and 50 mg.

(*Pyranisamine 8-bromtheophyllinate, Pyrabrom*)	E. L. Patch	Glybrom	Tablet	50 mg.
Neohetramine (Thonzylamine hydrochloride)	Wyeth	Neohetramine	Tablet	25, 50 and 100 mg
		Neohetramine	Liquid	6.25 mg./ml.
		Neohetramine Cream	Ointment	2%
Pyribenzamine (Tripelennamine hydrochloride)	Ciba	Pyribenzamine	Tablet	50 mg
		Pyribenzamine	Enteric coated	50 mg
		Pyribenzamine Elixir	Liquid	7.5 mg (citrate)/ml.
		Pyribenzamine Ointment	Ointment	2% (petrolatum base)
		Pyribenzamine Cream	Ointment	2% (water-washable base)
		Pyribenzamine-Ephedrine	Tablet	25 mg + 12 mg. ephedrine sulfate
		Pyribenzamine Expectorant with Ephedrine	Liquid	each 4 ml = 30 mg (citrate) + 10 mg ephedrine sulfate + 80 mg. ammonium chloride
		Pyribenzamine	Nasal Solution	0.5%
		Pyribenzamine	Injectable	25 mg/ml
		Pyribenzamine	Nebulizer	0.5%
Pyrrolazote (Pyrathiazine)	Upjohn	Pyrrolazote	Tablet	50 mg
		Pyrrolazote Elixir	Liquid	each ml = 2.5 mg + 10% alcohol + tolu balsam, glycerin and aromatics

		Thephorin Expectorant	Liquid	4 ml. = 10 mg. + 4 mg codeine phosphate + 4 mg papaverine hydrochloride + 30 mg ammonium chloride + 0.016 ml. chloroform
		Thephorin	Injectable	12.5 mg/ml.
Trimeton (Prophenpyridamine)	Organon	Cehistra	Effervescent Tablet	10 mg (maleate) + 100 mg. ascorbic acid + 320 mg. aspirin + 1,820 mg. sodium bicarbonate, calcium hydroxide, citric acid
	Schering	Trimeton	Tablet	25 mg.
		Trimeton Maleate Elixir	Liquid	4 ml. = 7.5 mg., 7% alcohol
		Trimeton Maleate Cream	Ointment	3%

meningoencephalomyelitis in the guinea pig, J. Immunol. 60 345, 1948

10 Ameline, A. Traitement de certaines dysménorrhées par les antihistaminiques de synthèse, Presse méd. 56 821, 1948.

11. Anderson, L. T; Gakenheimer, W. C.; Rosenblum, C., and Smith, E. H., Spectrophotometric assay method for pyranisamine maleate, J. Am. Pharm. A. 38:373, 1949.

12. Anrep, G V, Ayadi, M. S, Barsoum, G S.; Smith, J R., and Talaat, M. M. The excretion of histamine in urine, J. Physiol. 103 155, 1944.

13 Anrep, G V, Barsoum, G S., and Ibrahim, A. The histaminolytic action of blood during pregnancy, J Physiol. 106: 379, 1947

14 Arbesman, C. E. The pharmacology, physiology, and clinical evaluation of the new antihistaminic drugs (Pyribenzamine and Benadryl), New York State J. Med. 47 1775, 1947.

15 Arbesman, C. E. Comparative studies of several antihistaminic drugs, J. Allergy 19 178, 1948.

16. Arbesman, C. E., Cohen, V L., and Osgood, H. Pyribenzamine versus specific hyposensitization in the treatment of pollinosis A comparative study, J Allergy 18 311, 1947.

17 Arbesman, C. E., Koepf, G F, and Lenzner, A. R. Clinical studies with N'pyridyl, N'benzyl, dimethyletheylenediamine monohydrochloride (Pyribenzamine), J Allergy 17 275, 1946

18 Arbesman, C. E., Koepf, G F., and Miller, G E.. Some antianaphylactic properties of N'pyridyl, N'benzyl, dimethylethylenediamine monohydrochloride (Pyribenzamine), J. Allergy 17 203, 1946

19 Arbesman, C. E, Neter, E., and Becker, C. F · The effect of Pyribenzamine, Neohetramine and rutin on reversed anaphylaxis in guinea pigs, J Allergy 21 25, 1950

20 Arminio, J J, and Sweet, C. C. The prophylaxis and treatment of the common cold with Neohetramine (thonzylamine hydrochloride), Indust. Med & Surg. 18 509, 1949.

21. Ashford, C. A., Heller, H, and Smart, G A. The effect of antihistamine substances on gastric secretion in man, Brit. J Pharmacol 4 157, 1949

22 Baer, R. L., and Sulzberger, M. B · Pyribenzamine in the treatment of itching skin conditions, J Invest. Dermat. 7 147, 1946

37. Best, C. H., and McHenry, E. W · A note on histaminase, Canad. M. A. J 43:163, 1940
38 Bignall, J R., and Crofton, J Antihistamine drugs in treatment of nausea and vomiting due to streptomycin, Brit. M J 1.13, 1949.
39 Blackman, N S., and Hayes, J. C· Fatality associated with Benadryl therapy, J Allergy 19 390, 1948.
40 Blanton, W., and Owens, M. E. B, Jr. Granulocytopenia due probably to 'Pyribenzamine," J A. M. A. 134 454, 1947
41. Blumenthal, J S The antihistamine drugs in the treatment of hay fever in the adult, Journal Lancet 69 215, 1949.
42 Boquet, A. Substances antihistaminiques" et réactions tuberculiniques, Ann. Inst. Pasteur 69 55, 1943
43 Bordley, J E., Carey, R. A., Harvey, A. M , Howard, J E., Kattus, A. A., Newman, E. V , and Winkenwerder, W L. Preliminary observations on the effect of adrenocorticotropic hormone (ACTH) in allergic diseases, Bull. Johns Hopkins Hosp 85 396, 1949
44 Bordley, J E., Harvey, A. M. G , Howard, J E., and Newman, E. V Preliminary report on the use of ACTH in the hypersensitive state, in Mote, J R. (ed.) *Proceedings of the First Clinical ACTH Conference* (Philadelphia The Blakiston Company, 1950), p 469
45 Borman, M C Danger with Benadryl of self medication and large dosage, J A. M. A 133 394, 1947
46 Bourque, J E., and Loew, E R. The effect of histamine antagonists on gastric secretion, Am. J Physiol. 138 341, 1943
47 Bourquin, J B D'un novel antihistaminique de synthese (Antistine) et de ses applications en ophthalmologie, Schweiz. med Wchnschr 76 296, 1946
48 Bovet, D , Horclois, R., and Fournel, J L'antagonisme exerce par la N-p-méthoxybenzyl-N-diméthylaminoethyl α-aminopyridine sur l'hypotension et la vasodilatation histaminiques, Compt. rend Soc. de biol 138 165, 1944
49 Bovet, D , Horclois, R., and Walthert, F Propriétés antihistaminiques de la N-p-méthoxybenzyl-N-dimethylaminoethyl α amino-pyridine, Compt. rend Soc *de biol.* 138 99, 1944
50 Bovet, D., and Maderni, P· Action sympathicolytic de

R. C., and Sannella, T.: A clinical evaluation of chlorcyclizine (Perazil), Ann. Allergy 8.32, 1950
65. Brown, E. A., Weiss, L. R., and Maher, J. P.: The clinical evaluation of a new histamine antagonist "Decapryn," Ann. Allergy 6:1, 1948.
66. Brown, E. B., and Brown, F W.: The use of a new antihistaminic combination in the treatment of allergic disorders, New York State J Med. 48.1465, 1948.
67. Budnitz, J: The use of Benadryl in Parkinson's disease, New England J. Med. 238.874, 1948.
68. Bukantz, S. C., and Dammin, G J: Fluorescein as an indicator of antihistaminic activity: Inhibition of histamine-induced fluorescence in the skin of human subjects, Science 107 224, 1948
69. Burchell, H. B., and Varco, R. L. The antihistamine activity of thymoxyethyldiethylamine and N'-ethyl-N'-diethylaminoethylaniline as judged by the gastric response to histamine, J. Pharmacol. & Exper Therap. 75.1, 1942.
70. Bussell, L. Symptomatic treatment of myotonia atrophica, Brit. M. J 2 1206, 1949.
71. Cahan, A. M., Meilman, E., and Jacobson, B M. Agranulocytosis following Pyribenzamine, New England J Med 241 865, 1949.
72. Campaigne, E., and LeSuer, W. M. 3-substituted thiophenes: III Antihistamines of the N-(3-thenyl)-ethylenediamine series, J Am. Chem. Soc. 71 333, 1949
73. Campbell, B. Inhibition of anaphylactic shock by acetylsalicylic acid, Science 108 478, 1948.
74. Campbell, B, Baronofsky, I D., and Good, R. A. Effects of Benadryl on anaphylactic and histaminic shock in rabbits and guinea pigs, Proc. Soc. Exper. Biol. & Med. 64 281, 1947
75. Canterbury, E. A., and Feinberg, S M. Unpublished observations.
76. Carliner, P E., Radman, H. M, and Gay, L N.: Treatment of nausea and vomiting of pregnancy with Dramamine Preliminary report, Science 110 215, 1949
77. Carlson, R. G, and Whitehead, R. The effect of sodium, potassium and thiosulfate ions on anaphylaxis, J Allergy 14-462, 1943
78. Carryer, H M., and Koelsche, G. Use of antihistaminic

90 Code, C. F: The source in blood of the histamine-like constituent, J Physiol. 90.349, 1937.

91 Code, C. F.: The mechanism of anaphylactic and allergic reactions. An evaluation of the role of histamine in their production, Ann Allergy 2 457, 1944

92. Code, C. F, and Hester, H R. The blood histamine during anaphylactic shock in the horse and calf, Am J. Physiol. 127 71, 1939

93 Coffin, G S., and Kabat, E. A. The effects of immunization with histamine azoprotein on histamine intoxication and passive anaphylaxis in the guinea pig, J Immunol. 52 201, 1946.

94 Coffin, M. Intoxication mortelle par ingestion massive accidentelle d Antergan, Arch. Franç pediat. 4 374, 1947

95 Cohen, E B, Davis, H P, and Mowry, W A. Thephorin in allergy Study of 292 cases, Am. J. Med 5 44, 1948

96 Cohen, M. B, and Friedman, H J Histamine azoprotein in the treatment of allergy, J Allergy 18 7, 1947.

97. Combes, F C., Zuckerman, R., and Canizares, O.. Diatrin hydrochloride Clinical and toxicological studies of a new antihistaminic agent, J Invest. Dermat. 13 139, 1949

98 Committee on Therapy of the American Academy of Allergy Report, J Allergy 20 310, 1949

99 Committee on Therapy of the American Academy of Allergy. Report, J Allergy 21 255, 1950

100 Cortes, J L., and Rodriguez Herrera, E. Effectos de las ionizaciones de Benadryl en kjidos con manifestaciones alergicas, Alergia 2 1, 1948

101 Council on Pharmacy and Chemistry, American Medical Association Too many drugs, J A. M. A. 139.378, 1949

102. Council on Pharmacy and Chemistry, American Medical Association Report of the Council Status report on antihistaminic agents in the prophylaxis and treatment of the common cold,' J A. M A. 142 566, 1950

103 Court Brown, W M., and Hunter, R. B: Antihistamine drugs and radiation sickness, Brit. M. J 2 984, 1948

103a. Cowan, D. W, and Diehl, H. S Antihistaminic agents and ascorbic acid in the early treatment of the common cold, J A. M A 143 421, 1950

104 Craig, J, Clark, N S, and Chalmers, J. D. Antihistaminic drug treatment of acute nephritis, Brit. M. J 1 6, 1949

Dale, H. H., and Laidlaw, P. P.: The physiological action of β iminazolylethylamine, J. Physiol. 41:318, 1911.

9 Dammin, G. J., and Bukantz, S. C.: Modification of biologic response in experimental hypersensitivity, J. A. M. A. 139: 358, 1949.

9a Dannenberg, T. B., and Feinberg, S. M.: Unpublished observations.

0 Darsie, M. L., Jr.; Perry, S. M., Rosenfeld, D., and Zaro, J. A.: Size of histamine wheal in relation to dose and to animal species, Proc. Soc. Exper. Biol. & Med. 59:278, 1945.

1 D'Avanzo, C. S.: Thephorin ointment in pruritic dermatoses, New England J. Med. 241:741, 1949.

2 Davis, J. H., and Hunt, H. H.: Accidental Benadryl poisoning. Report of a fatal case, J. Pediat. 34:358, 1949.

23 Decourt, J.: Le médication antihistaminique, Semaine d. hôp. Paris 21:707, 1945.

24. Decourt, J., Rimiers, A., and Sonnet, P.: Antihistaminiques de synthèse et secrétion histaminique de l'estomac, Compt. rend. Soc. de biol. 139:470, 1945.

25 Decourt, P.: Action de bases antagonistes de l'histamine sur quelques maladies liées à des réactions d'hypersensibilité, Bull. et mém. Soc. méd. d. hôp. de Paris 58:265, 1942.

26. Deichman, W. B.: Notes from the pharmacy committee, Division of Pharmacology, Albany Medical College, 1950.

127 Omitted

128 Deutsch, E.: Ueber die Wirkung von Antihistaminsubstanzen auf den Magensaft des Menschen, Klin. Med., Wien 2:1113, 1947.

129 Dews, P. B., and Graham, J. D. P.: The antihistamine substance 2786RP, Brit. J. Pharmacol. 1:278, 1946.

130 Diehl, H. S., Baker, A. B., and Cowan, D. W.: Cold vaccines. Evaluation based on controlled study, J. A. M. A. 111:1168, 1938.

131 Dill, W. A., and Glazko, A. J.: Biochemical studies on diphenhydramine (Benadryl). I. Chemical determination of diphenhydramine, J. Biol. Chem. 179:395, 1949.

132. Dougray, T.: Antihistamines in the treatment of nausea and vomiting of pregnancy, Brit. M. J. 2:1081, 1949.

133 Dragstedt, C. A.: The significance of histamine in anaphylaxis and allergy, Quart. Bull., Northwestern Univ. M. School 17:102, 1943.

tients with collagen and allied diseases, in Mote, J R. (ed): *Proceedings of the First Clinical ACTH Conference* (Philadelphia The Blakiston Company, 1950), p. 429.

1 Ellis, F A., and Bundick, W. R · Reactions to the local use of Thephorin, J. Invest. Dermat. 13·25, 1949

2. Ellis, F. W The effects of some new spasmolytic agents in perfused guinea pig lungs, Federation Proc. 4 117, 1945.

53 Elster, S K., Freeman, M. E., and Lowry, E. L The action of tripelennamine on hyaluronidase in the albino rat, J Pharmacol. & Exper Therap 96 332, 1949

54 Emmelin, N, and Muren, A. Effects of antihistamine compounds on the adrenaline liberation from the suprarenals, Acta physiol. Scandinav 17 345, 1949

55 Engelsher, D L Antihistamine drugs in asthma and hay fever, New York State J Med 47 1686, 1947

56 Epstein, E Dermatitis occurring during therapy with tripelennamine hydrochloride (Pyribenzamine hydrochloride), J A. M. A. 134 782, 1947.

157 Epstein, E Dermatitis due to antihistaminic agents, J. Invest. Dermat. 12 151, 1949

158 Ercoli, N, Schachter, N, Hueper, R. J, and Lewis, M N · *The toxicologic and antihistaminic properties of* N,N'-dimethyl-N' phenyl N'-(2 thienylmethyl) ethylenediamine hydrochloride (Diatrin), J Pharmacol. & Exper Therap 93. 210, 1948

159 Ercoli, N, Schachter, R. J, Leonard, F., and Solmssen, U V. A new antihistaminic N,N-dimethyl-N'-(2-pyridyl)-N'-(2-thienylmethyl)-ethylenediamine hydrochloride, Arch. Biochem 13 487, 1947

160 Essex, H E, and Horton, B T Observations on development of resistance to histamine in the guinea pig, Proc Staff Meet, Mayo Clin. 16 603, 1941.

161 Essex, H E., Wegria, R. G, Herrick, J F, and Mann, F C., The effect of certain drugs on the coronary blood flow of the trained dog, Am. Heart J 19 554, 1940

162 Eyermann, C. H Clinical experiences with a new antihistaminic drug, J Allergy 17 210, 1946

163 Fabinyi, M, and Szebehelyi, J The mechanism of desensitization with histamine, Acta allergol. 2 233, 1949

164 Fabricant, N D Personal communication

165 Farber, S, Pope, A, and Landsteiner, E., Jr. Role of acetyl-

0. Feinberg, S. M.: Pyrrolazote. Unpublished observations.
1. Feinberg, S. M., and Bernstein, T. B.: Tripelennamine "Pyribenzamine" ointment for the relief of itching, J. A. M. A. 134 874, 1947.
2. Feinberg, S M., and Bernstein, T. B · Histamine antagonists: VIII. N-(α-pyridyl)-N-(α-thienyl)-N', N-dimethylethylenediamine, a new antihistaminic compound; experimental and clinical experiences, J. Lab & Clin. Med. 32.1370, 1947.
33 Feinberg, S. M., and Bernstein, T. B. Histamine antagonists: X. A new antihistaminic drug, 2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl]-pyridine succinate (Decapryn succinate), experimental and clinical results, J. Lab. & Clin. Med. 33 319, 1948.
84. Feinberg, S M., and Bernstein, T. B.: Nebulized Pyribenzamine in nasal and bronchial allergy, J. Lab. & Clin. Med. 34:1078, 1949
185. Feinberg, S M., and Friedlaender, S · Relief of dermographism and other urticarias of histamine origin by a synthetic benzhydryl alkamine ether, J Allergy 16 296, 1945.
186. Feinberg, S. M., and Friedlaender, S Histamine antagonists· IV. Pyridyl-N'-benzyl-N-dimethylethylenediamine (Pyribenzamine) in symptomatic treatment of allergic manifestations, Am. J M. Sc. 213 58, 1947.
187. Feinberg, S. M., Malkiel, S; Bernstein, T B, and Hargis, B. J. Histamine antagonists XV. Comparative experimental studies of certain antihistaminic compounds, J Pharmacol. & Exper Therap, in press.
188 Feinberg, S M., Malkiel, S, and Dannenberg, T. B.· Unpublished observations
189. Feinberg, S M., Norén, B, and Feinberg, R. H.· Histamine antagonists XI. Aerosolized antihistamine drugs in prevention of histamine bronchospasm in guinea pigs, J. Allergy 19 90, 1948.
190 Feinstone, W H, Williams, R. D., and Rubin, B.· Antihistamine and antianaphylactic effect of Hetramine, Proc. Soc. Exper. Biol. & Med. 63.158, 1946.
191. Fell, N, Rodney, G., and Marshall, D. E.: Histamine-protein complexes, synthesis and immunologic investigation: I. Histamine-azoprotein, J. Immunol. 47·237, 1943.
192. Feller, A. E.; Badger, G. F., Hodges, R. G; Jordon, W. S.; Rammelkamp, C. H., and Dingle, J. H.: The failure of anti-

Relationship to ultraviolet erythema, J Allergy 20 229, 1949

H. Friedlaender, S, and Feinberg, S M.: *Histamine antagonists.* III. The effect of oral and local use of β-dimethylaminoethyl benzhydryl ether hydrochloride on the whealing due to histamine, antigen-antibody reactions, and other whealing mechanisms Therapeutic results in allergic manifestations, J Allergy 17 129, 1946.

05 Friedlaender, S, Feinberg, S. M., and Feinberg, A. R. Histamine antagonists V. Comparison of Benadryl and Pyribenzamine in histamine and anaphylactic shock, *Proc. Soc.* Exper. Biol. & Med. 65 65, 1946

206. Friedlaender, S, Feinberg, S M., and Feinberg, A. R. Histamine antagonists VI. Comparative antihistaminic activity of some ethylenediamine drugs in the guinea pig, J Lab & Clin. Med. 32 47, 1947

207. Friedlaender, S, and Friedlaender, A S Experimental and clinical studies of Neohetramine, a new antihistaminic agent, *J Lab & Clin.* Med 33 865, 1948

208. Friedlaender, S., and Friedlaender, A. S Parenteral Benadryl in allergy, Am. J Med 4 863, 1948

209 Friedman, E., and Silverman, I. The effect of antihistamine medication on the tuberculin reaction in children, Am. Rev. Tuberc. 60 354, 1949

210 Friedman, L. The use of aerosol 'Benadryl" in bronchial asthma, South. M. J 42 491, 1949

211 Friesen, S R., Baronofsky, I D, and Wagensteen, O. H.. Benadryl fails to protect against histamine provoked ulcer, Proc. Soc. Exper Biol. & Med. 63 23, 1946

212 Fuchs, A. M., Schulman, P M., and Strauss, M. B. Clinical studies with Pyribenzamine (N'-pyridyl-N'benzyl-N-dimethylethylenediamine) in hay fever, J Allergy 18.385, 1947

213 Gair, D S, and Ducey, J Chemical structure of substances effective in treatment of parkinsonism, Arch. Int. Med 85 284, 1950

214. Gastineau, C. F., and Leavitt, M. D. Treatment of allergy to insulin Report of one case, *Proc. Staff Meet.*, Mayo Clin. 21 316, 1946.

215 Gaté, J, Thiers, H, Cuilleret, P., and Pellerat, J Recherches

phenhydramine (Benadryl): II Distribution in tissues and urinary excretion, J. Biol. Chem. 179.403, 1949.

9 Glazko, A. J., and Dill, W. A. Biochemical studies on diphenhydramine (Benadryl): IV. Degradation of Benadryl by tissue enzymes, J. Biol. Chem. 179 417, 1949

0. Glazko, A. J, McGinty, D A., Dill, W. A., and Ward, C. S: Biochemical studies on diphenhydramine (Benadryl): III. Application of radioactive carbon to metabolic studies of Benadryl, J. Biol. Chem. 179 409, 1949

31 Goldberg, L. C.: The treatment of dermatoses with Benadryl (β-dimethylaminoethyl benzhydryl ether hydrochloride): An analysis of its effects upon 170 patients with various dermatoses, J Invest. Dermat. 7:301, 1946

32. Goldman, H L Clinical evaluation of Trimeton, J Maine M. A. 40 111, 1949.

33 Goldman, R.; Adams, W S; Beck, W S, Levin, M.; Bassett, S. H., and White, A. The effect of ACTH on one case of periarteritis nodosa, in Mote, J R. (ed.) *Proceedings of the First Clinical ACTH Conference* (Philadelphia: The Blakiston Company, 1950), p 437.

234 Gordon, J S Antihistaminic drugs in the treatment of upper respiratory tract infection, Laryngoscope 58 1265, 1948.

235 Grant, W M., and Loeb, D. R. Effect of locally applied antihistamine drugs on normal eyes, Arch. Ophth. 39 553, 1948.

236. Graub, M., and Battist, E. M. The effect of antihistaminic drugs upon the tuberculin reaction, Am. Rev Tuberc. 61: 735, 1950

237. Gunnar, R. M., and Weeks, R. E. Effect of tripelennamine hydrochloride on burn shock, Arch. Path. 47:594, 1948.

238. Guy, W B The effect of Pyribenzamine on the tuberculin reaction in man, J Invest. Dermat. 8.335, 1947.

239. Haley, T J Microtoxicology II Identification and differentiation of Benadryl and Pyribenzamine hydrochloride, J. Am Pharm. A. 37 294, 1948

240 Haley, T J., and Harris, D H. The effect of topically applied antihistaminic drugs on the mammalian capillary bed, J Pharmacol. & Exper. Therap. 95 293, 1949

241 Haley, T J, and Harris, D. H. The effect of several antihistaminic drugs on mortality due to x-irradiation, Stanford M. Bull. 8 1, 1950.

histamine substance derived from phenothiazine (Phenergan, 3277RP), Canad. M A. J 59-322, 1948.
5 Halpern, B N, Hamburger, J., and Cruchaud, S: Action préventive d'un antihistaminique dérivé de la thiodiphénylamine sur l'oedème aigu du poumon expérimental, Acta allergol 1 97, 1948
6. Halpern, B, Hamburger, J., and Cruchaud, S · Action préventive d un antihistaminique dérivé de la thiodiphénylamine sur l oedème aigu du poumon experimental, Semaine d hôp Paris 24 656, 1948
57 Halpern, B, Hamburger, J, and Debray, C. Note préliminaire sur une nouvelle serie chimique de corps doués d'une activité antihistaminique et antiallergique puissante Les dérives de la thiodiphenylamine, Bull. et mém. Soc méd d. hôp de Paris 62 607, 1946.
58 Halpern, B N, and Laubscher, J P Recherches sur l'action des antihistaminiques de synthèse sur la resistance capillaire chez l'homme, Semaine d hop Paris 21 667, 1948
259 Halpern, B N, Perrin, G., and Dews, P Pouvoir anesthésique local de quelques antihistaminiques de synthèse· Relations entre l action anesthesique et l action antihistaminique, Compt rend Soc. de biol. 141 1125, 1947
260 Halpern, B N, Perrin, G, and Dews, P B, Pouvoir anesthésique local de quelques antihistaminiques de synthèse Relation entre l'action anesthésique et l action antihistaminique, Semaine d hop Paris 24 2561, 1948
261 Halpern, B N, and Walthert, F Conditionnement de l antagonisme histamine-antihistaminiques sur la corne utérine de cobaye par l équilibre ionique du milieu de survie, Compt rend Soc de biol 139 402, 1945
262 Hamburger, J, Halpern, B N, and Neel, J Action préventive de l antihistaminique de synthèse N-diméthylamino-2 propyl-1-thiodiphenylamine (3277RP) sur l albuminurie orthostatique experimentale, Compt. rend Soc. de biol. 142 183, 1948
263 Hare, R. An experimental investigation into the vascular reactions of the susceptible skin to protein, Heart 13 227, 1926
264 Harris, M C., and Shure, N Eczematoid dermatitis following ingestion of 'Pyribenzamine hydrochloride' N.N.R. tablets, J Allergy 18 408, 1947

histamine substance derived from phenothiazine (Phenergan, 3277RP), Canad. M. A. J 59 322, 1948

255 Halpern, B N; Hamburger, J., and Cruchaud, S. Action préventive d'un antihistaminique dérivé de la thiodiphénylamine sur l'oedème aigu du poumon expérimental, Acta allergol. 1 97, 1948

256 Halpern, B, Hamburger, J, and Cruchaud, S Action préventive d'un antihistaminique dérivé de la thiodiphénylamine sur l'oedème aigu du poumon experimental, Semaine d. hôp Paris 24 656, 1948

257 Halpern, B, Hamburger, J., and Debray, C. Note préliminaire sur une nouvelle serie chimique de corps doues d'une activité antihistaminique et antiallergique puissante: Les dérivés de la thiodiphénylamine, Bull. et mém. Soc. med. d. hôp de Paris 62 607, 1946.

258 Halpern, B N., and Laubscher, J P Recherches sur l'action des antihistaminiques de synthèse sur la resistance capillaire chez l'homme, Semaine d. hôp Paris 21 667, 1948.

259 Halpern, B. N, Perrin, G, and Dews, P Pouvoir anesthésique local de quelques antihistaminiques de synthèse. Relations entre l'action anesthesique et l'action antihistaminique, Compt. rend Soc. de biol. 141 1125, 1947.

260 Halpern, B N, Perrin, G, and Dews, P B, Pouvoir anesthésique local de quelques antihistaminiques de synthèse. Relation entre l'action anesthésique et l'action antihistaminique, Semaine d hôp Paris 24 2561, 1948

261 Halpern, B N, and Walthert, F Conditionnement de l'antagonisme histamine-antihistaminiques sur la corne utérine de coboye par l'equilibre ionique du milieu de survie, Compt rend. Soc. de biol. 139 402, 1945

262. Hamburger, J, Halpern, B N, and Neel, J Action préventive de l'antihistaminique de synthèse N-diméthylamino-2-propyl-1-thiodiphénylamine (3277RP) sur l'albuminurie orthostatique expérimentale, Compt. rend. Soc. de biol. 142 183, 1948

263 Hare, R. An experimental investigation into the vascular reactions of the susceptible skin to protein, Heart 13 227, 1926

264 Harris, M. C., and Shure, N Eczematoid dermatitis following ingestion of "Pyribenzamine hydrochloride" N N R. tablets, J Allergy 18 408, 1947

mine on the respiration of mouse brain homogenates, J Lab. & Clin. Med. 35.284, 1950.

278 Hüllstrung, H., and Hach, K.· Experimentelle Sensibilisierung und deren Beeinflussung durch Vitamine beim Meerschweinchen· I, Ztschr. f. Immunitätsforsch. u. exper. Therap 100 393, 1941.

279 Hunter, R. B. Neoantergan in the treatment of urticaria, Lancet 1 672, 1947

280 Hunter, R. B., and Dunlop, D. M.· Antihistamine drug for pruritus of jaundice, Brit. M. J. 2·547, 1947

281 Hunter, R. B., and Dunlop, D. M., A review of antihistamine drugs, Quart. J Med. 17.271, 1948.

282 Hurwitz, P.: Antistine in ocular allergy, Am. J. Ophth. 31:1409, 1948

283 Hutter, C. P · Chemistry of antihistamine substances, Enzymologia 12:277, 1948

284 Hutter, C. P; Djerassi, C.; Beears, W. L.; Mayer, R. L., and Scholz, C. R.. Heterocyclic amines with antihistaminic activity, J Am. Chem. Soc. 68 1999, 1946.

285 Ingraham, R. C., and Wiggers, H. C. Treatment of impending hemorrhagic shock with an antihistamine agent, Federation Proc. 5 50, 1947.

286 Jacques, L. B., and Waters, E. T The isolation of crystalline heparin from the blood of dogs in anaphylactic shock, Am. J. Physiol. 129 398, 1940

287 Janowitz, H., and Grossman, M. I. Minimal effective dose of intravenously administered histamine in pregnant and non pregnant human beings, Am. J Physiol. 157 94, 1949.

288 Jaros, S H. The clinical application of a new piperazine compound II. Clinical observations, Ann. Allergy 7 466, 1949

289 Jaros, S H.; Castillo, J C., and de Beor, E. J The clinical application of a new piperazine compound I. Human pharmacology, Ann. Allergy 7.458, 1949

290 Jones, H. M., and Brady, E. S The colorimetric estimation of N(2-pyridyl) substituted antihistamine drugs, J Am. Pharm. A. 38 579, 1949

291 Judd, A. R., and Henderson, A. R. The use of antihistaminic drugs in human tuberculosis, Ann Allergy 7 306, 1949

with Pyribenzamine hydrochloride, Ann. Allergy 6:408, 1948

309 Kesten, B M., and Sheard, C., Jr. Treatment of allergic and some other dermatoses with Thephorin, J. Invest. Dermat. 9 65, 1947.

310 Kline, P R., and Baer, R L. Nature of inhibition of ultraviolet erythema by Pyribenzamine Preliminary report, J Invest. Dermat. 10 397, 1948

311 Koelsche, G A., Prickman, L. E., and Carryer, H M. The symptomatic treatment of bronchial asthma and hay fever with Benadryl, Proc. Staff Meet., Mayo Clin 20 432, 1945.

312. Kreis, B Action d'un anti-histaminique de synthèse sur l'allergie tuberculeuse du cobaye, Ann Inst. Pasteur 72 308, 1946

313 Krueger, A. A. Histamine in treatment of allergic diseases: A report of 126 cases, Northwest Med 47 27, 1948

314 Kyrides, L. P, Meyer, F C., and Zienty, F B Thiophene-containing antihistaminic agents, J Am. Chem. Soc. 69 2239, 1947

315 Kyser, F A. Recent studies on experimental myocarditis, Quart. Bull., Northwestern Univ M. School 22 256, 1948

316. Kyser, F A., McCarter, J C., and Stengle, J Effect of antihistamine drugs (including Benadryl) upon serum-induced myocarditis in rabbits, J Lab & Clin. Med 32 379, 1947

317 Labelle, A., and Tislow, P. Pharmacological properties of Trimeton, a new antihistaminic compound, Federation Proc. 7 236, 1948

318 Landau, S W, and Gay, L. N Influence of certain amino acids on histamine reactions and anaphylactic reactions in intestinal strips of guinea pigs and in intact guinea pigs, Bull. Johns Hopkins Hosp 74 55, 1944

319 Landau, S W, and Gay, L. N Comparative study of antihistamine substances I Introduction and Dale experiments, Bull Johns Hopkins Hosp 83 330, 1948

320 Landau, S W, Marriott, H J L., and Gay, L. N Comparative study of antihistamine substances II. Activity in vivo against histamine intoxication and anaphylactic shock of guinea pigs, Bull Johns Hopkins Hosp 83 343, 1948.

321 Lands, A. M, Hoppe, J O, Siegmund, O H, and Luduena, F P The pharmacological properties of three new anti-

with Pyribenzamine hydrochloride, Ann. Allergy 6:408, 1948

309 Kesten, B M., and Sheard, C., Jr Treatment of allergic and some other dermatoses with Thephorin, J Invest. Dermat. 9 65, 1947.

310 Kline, P. R., and Baer, R. L. Nature of inhibition of ultraviolet erythema by Pyribenzamine: Preliminary report, J. Invest. Dermat. 10 397, 1948

311 Koelsche, G A., Prickman, L. E., and Carryer, H. M. The symptomatic treatment of bronchial asthma and hay fever with Benadryl, Proc. Staff Meet., Mayo Clin 20 432, 1945.

312 Kreis, B Action d'un anti-histaminique de synthèse sur l'allergie tuberculeuse du cobaye, Ann. Inst. Pasteur 72 308, 1946.

313 Krueger, A. A Histamine in treatment of allergic diseases: A report of 126 cases, Northwest Med. 47 27, 1948

314. Kyrides, L. P, Meyer, F C., and Zienty, F B. Thiophene-containing antihistaminic agents, J Am Chem Soc. 69. 2239, 1947

315 Kyser, F A Recent studies on experimental myocarditis, Quart. Bull., Northwestern Univ M. School 22 256, 1948.

316. Kyser, F A., McCarter, J C., and Stengle, J Effect of antihistamine drugs (including Benadryl) upon serum-induced myocarditis in rabbits, J Lab & Clin Med 32 379, 1947.

317 Labelle, A., and Tislow, P Pharmacological properties of Trimeton, a new antihistaminic compound, Federation Proc. 7 236, 1948

318 Landau, S W, and Gay, L. N Influence of certain amino acids on histamine reactions and anaphylactic reactions in intestinal strips of guinea pigs and in intact guinea pigs, Bull Johns Hopkins Hosp 74 55, 1944

319 Landau, S W, and Gay, L. N Comparative study of antihistamine substances I Introduction and Dale experiments, Bull Johns Hopkins Hosp. 83 330, 1948

320 Landau, S W, Marriott, H. J L., and Gay, L. N Comparative study of antihistamine substances II Activity in vivo against histamine intoxication and anaphylactic shock of guinea pigs, Bull. Johns Hopkins Hosp 83 343, 1948

321. Lands, A. M., Hoppe, J O, Siegmund, O. H, and Luduena, F D The pharmacological properties of three new anti-

the use of Benadryl A new antihistamine substance, Proc. Staff, Meet., Mayo Clin 20 417, 1945.

363 McEvedy, M. B Treatment of seasickness aboard ocean-going ships, Lancet 1 825, 1949

364 McGavack, T H, Drekter, I J.; Schutzer, S, and Heisler, A. Levels for Pyribenzamine and Benadryl in blood and urine following a single orally administered dose, J Allergy 19 251, 1948

365 McGavack, T. H., Elias, H., and Boyd, L. J The influence of dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) upon normal persons and upon those suffering from disturbances of the autonomic nervous system, J Lab. & Clin. Med 31 560, 1946.

366 McGavack, T H, Elias, H, and Boyd, L. J Some pharmacological and clinical experiences with dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl), Am. J M Sc 213 418, 1947

367 McGavack, T H, Schulman, P, Schutzer, R., and Elias, H. Effects of topical applications of diphenhydramine hydrochloride (Benadryl), Arch. Dermat. & Syph 57 308, 1948

368 MacGregor, A. G, and Wood, D R. The effect of Neo-antergan and of Benadryl on serum-induced myocarditis in rabbits, Brit J Pharmacol 4 216, 1949

369 Macht, M. B, Bader, M., and Mead, J The inhibition of frostbite wheals by the iontophoresis of antihistaminic agents, J Clin Investigation 28 564, 1949

370 McIntire, F C., Roth, L. W, and Shaw, J L The purification of histamine for bioassay, J Biol. Chem 170 537, 1947

371 Mackmull, G The influence of intravenously administered Benadryl on blood pressure and electrocardiogram, J. Allergy 19 365, 1948.

372 McMaster, P D., and Kruse, H Peripheral vascular reactions in anaphylaxis of the mouse, J Exper. Med 89 583, 1949

373 Macy, D, Jr, and Horton, B T Treatment of migraine with histamine Review of 144 cases, J. A. M. A. 137 1110, 1948

374 Maietta, A. L. Unusually good results in pollinosis with combined antigen-antihistamine therapy, shortening the treatment of hay fever, Ann. Allergy 7 789, 1949.

idyl N'-benzyl-N-dimethylethylenediamine HCl), an antagonist of histamine, J Lab & Clin. Med. 31:749, 1946.

390. Mayer, R. L.; Huttrer, C. P., and Scholz, C. R.: Antihistaminic and antianaphylactic activity of some α-pyridinoethylenediamines, Science 102·93, 1945.

391 Mayer, R. L., and Kull, F C.: Influence of Pyribenzamine and Antistine upon the action of hyaluronidase, Proc. Soc. Exper. Biol. & Med. 66 392, 1947.

392 Mayo Foundation for Medical Education and Research: Benadryl symposium, Proc. Staff Meet., Mayo Clin. 20 417, 1945

393 Meier, R., and Bucher, K.. Pharmakologie des 2-(N-phenyl-N-benzylaminomethyl)-imidazoline (Antistine), Schweiz. med. Wchnschr 76 294, 1946

394. Middleton, J W, and Rider, J A Antihistamines in the treatment of the common cold A preliminary report, Dis. of Chest 16 879, 1949.

395. Miller, J The parenteral use of Neo-Antergan, Ann Allergy 8 68, 1950.

396. Millner, T., and Hurst, A.. Tuberculosis and antihistaminics, Dis. of Chest 16 870, 1949.

397. Moersch, R. U, Rivers, A. B, and Morlock, C. G. Some results of the gastric secretory response of patients having duodenal ulcer noted during the administration of Benadryl, Gastroenterology 7 91, 1946

397a. Monash, D · Personal communication

398 Monchek, M. Clinical experiences with a new antihistaminic drug Thephorin, Journal Lancet 68·428, 1948.

399 Morris, H C., and Dragstedt, C. A. The antihistamine effect of imidazol, Proc. Soc. Exper Biol. & Med. 59 311, 1945.

400 Moseley, V The use of tripelennamine hydrochloride (Pyribenzamine) as a topical anesthetic, Am. J Digest. Dis. 15: 410, 1948

401 Mosko, M. M., and Peterson, W. L.. Sensitization to Antistine, J. Invest. Dermat. 14 1, 1950

402 Moynahan, E. J., and Watson, O Failure of antihistamine drugs to inhibit hyaluronidase in vitro, Nature, London 163 173, 1949

403 Murray, H G The treatment of head colds with an antihistaminic drug, Indust Med. 18 215, 1949.

Effects of various modes of administration of Pyribenzamine on the histamine wheal and epidermal sensitivity reactions, J. Invest. Dermat. 14:177, 1950.

418 Pettte, J D., and Mothersill, M. H.: Treatment of allergic symptoms with a new antihistamine drug, J. Indiana M. A. 40 739, 1947.

419 Pellerat, M. J., and Murat, M.: L'histamine cutanée. Ses variations sous l'influence du froid, au cours de l'allergie tuberculinique et dans certaines dermatoses, Ann. de dermat. et syph. 6 76, 1946

420. Pennypacker, C. S., and Sharples, I · Clinical study of a new antihistaminic drug, Thephorin, Pennsylvania M. J. 51 1407, 1948.

421 Perlman, E. A quantitative method for the determination of antihistaminic compounds containing the pyridine radical, J Pharmacol. & Exper. Therap 95.465, 1949.

422 Perry, D J The local use of Benadryl ointment, J. Invest. Dermat. 9 95, 1947

423 Perry, D J., Falk, M. S, and Pilsbury, D M. A comparison of the effect of antihistamine drugs in human subjects by means of histamine iontophoresis, J Invest. Dermat. 11.461, 1948.

424 Perry, D. J, and Hearin, D L. Experimental determination in human subjects of the duration of "antihistaminic" activity of orally administered compounds, J Invest. Dermat. 13 29, 1949

425 Peters, J A., Horton, B T., and Boothby, W. M. The effect of continuous intravenous administration of histamine on basal metabolism in human beings, J Clin. Investigation 24 611, 1945.

426 Peterson, J C., and Bishop, L. K. The treatment of serum sickness with Benadryl, J A. M A. 133:1277, 1947.

427. Phillips, W F P., and Fishbein, W. I. An antihistaminic analgesic preparation in the therapy of colds Final report, Indust. Med & Surg. 19 201, 1950

428. Portier, P., and Richet, C. De l'action anaphylactique de certains venins, Compt. rend. Soc. de biol. 54 170, 1902.

429. Poulsen, H. Antihistaminica som Antidot mod curarepraeparaters histaminliguende Virkning, Nord. med. 41·627, 1949.

430 Pratt, A. G · Paradoxic effect of antihistamine drug, Arch. Dermat. & Syph. 61:667, 1950

stration that periarteritis nodosa is a manifestation of hypersensitivity, Bull. Johns Hopkins Hosp. 72.65, 1943.

445 Rieveschl, G., and Gruhzit, O M. A toxicologic study of histamine antagonist β-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl), Federation Proc. 4 150, 1945.

446. Rigdon, R. H Effect of antihistamine on the localization of trypan blue in xylene-treated areas of the skin, Proc. Soc. Exper Biol. & Med. 71 637, 1949

447. Rives, H. F, Ward, B H, and Hicks, M L. A fatal reaction to methapyrilene (Thenylene), J A. M. A. 140.1022, 1949.

448 Roberts, R. C., Crockett, K. A., and Laipply, T. C. Effects of salicylates and Benadryl on experimental anaphylactic hypersensitive vascular and cardiac lesions, Arch. Int. Med. 83 48, 1949

449 Rocha e Silva, M. Recent advances concerning the histamine problem, J Allergy 15 399, 1944

450 Rocha e Silva, M. Inhibition of histamine effects by compounds of histamine, histidine and arginine, J Pharmacol. & Exper Therap 80 399, 1944.

451 Rodney, G, and Fell, N Histamine protein complexes: Synthesis and immunological investigation II β-(5-imidazolyl)-ethyl carbamide protein, J Immunol 41 251, 1943.

452 Rose, B Production of symptoms by subcutaneous injection of histamine without increase of the blood histamine, Science 92 454, 1940

453 Rose, B Studies on blood histamine in patients with allergy II Alterations in the blood histamine in patients with allergic disease, J Clin. Investigation 20 419, 1941

454 Rose, B Studies on the effect of ACTH on eosinophilia and bronchial asthma, in Mote, J R. (ed) *Proceedings of the First Clinical ACTH Conference* (Philadelphia, The Blakiston Company, 1950), p 491.

455 Rose, B Unpublished observations

456 Rose, B, Entin, M., and Baxter, H. In press

457 Rose, B, Harkness, E. V., and Forbes, R. P Plasma histaminase in pregnancy, 1946 Annual Report of the John and Mary R. Markle Foundation, p 69

458 Rose, B, Harkness, E. V., and Forbes, R. P Plasma histaminase, 1947 Annual Report of the John and Mary R. Markle Foundation, p 69

action of rutin in anaphylactic and histamine shock, Science 108 410, 1948.
472. Rothman, S., and Henningsen, A B · The sunburn protecting effect of para-aminobenzoic acid, J. Invest. Dermat. 9 307, 1947.
472a. Rubin, S S; Kaplan, M. A., Aaronson, A. L., and Feinberg, S M · Potassium salts in the treatment of pollinosis · A clinical evaluation, J A. M. A. 114 2359, 1940.
473 Rubinsky, H J, Bresnick, E., Levinson, L., Risman, G, and Segal, M S · Parenteral and aerosol administration of antihistaminic agent in the treatment of severe bronchial asthma, New England J Med. 241 853, 1949
474 Ryan, G M S., and Wood, J S.· Benadryl in the treatment of parkinsonism, Lancet 1 258, 1949
475 Sachs, B A. The toxicity of Benadryl Report of a case and review of the literature, Ann Int Med. 29 135, 1948.
476 St. Karady, and Bentsah, A. Die Prophylaxe der Kollapsbereitschaft durch kunstliche Veränderung der Histaminempfindlichkeit, Ztschr f klin Med 128 640, 1935
477. Sangster, W, Grossman, M. I, and Ivy, A. C. The effect of two new histamine antagonists (Benadryl and compound 63) on histamine stimulated gastric secretion in the dog, Gastroenterology 6 436, 1946
477a. della Santa, R., Plattner, H. C., and de Beule, R., Antihistaminique de synthèse et résistance capillaire, Rev. méd. de la Suisse Rom. 67 716, 1947
478 Saiber, R. W Effect of Benadryl hydrochloride on the tuberculin reaction in guinea pigs, Am. Rev Tuberc. 57 504, 1948.
479 Schiller, I W, and Lowell, F C. Trimeton, a new antihistamine drug, New England J Med 240 215, 1949
480 Schindler, O Klinische Untersuchungen mit der Antihistaminsubstanz Antistin Ciba, Schweiz. med. Wchnschr. 76 300, 1946
481 Schwartz, E. Comparative toxicity and side effects of the antihistamine drugs, Ann Allergy 7 770, 1949
482 Schwartz, E., and Leibowitz, H · Local nasal therapy with Pyribenzamine in seasonal and nonseasonal hay fever, J. Allergy 20 269, 1949
483. Schwartz, E., Levin, L., and Wallman, M. Clinical evaluation of thenylpyramine hydrochloride (Histadyl) in the

neal reflex of rabbits, Univ. Hosp Bull., Ann Arbor 15:42, 1949.

499 Sheldon, J. M.; Weller, K. E; Haley, R. R., and Fulton, J K.. Clinical observations with Decapryn, a new antihistaminic compound, Univ Hosp Bull., Ann Arbor 14:13, 1948

500 Sherman, J., and Walzer, E. H.: The responsiveness of human skin to histamine introduced by the electrophoretic technic, J Invest. Dermat. 9 187, 1947.

501. Sherman, W. B., and Cooke, R. A.. Dermatitis following the use of Pyribenzamine and Antistine, J Allergy 21 63, 1950.

502. Sherrod, T. R.; Loew, E. R., and Schloemer, H. F.· Pharmacological properties of antihistamine drugs Benadryl, Pyribenzamine and Neo-Antergan, J Pharmacol. & Exper Therap 89 247, 1947.

503 Shibata, S · Beeinflussung der Darmreaktion des Histamins durch Verschiedene Aminosäuren, Osaka Igk. Z. 39 549, 1940 (abst., Jap. J. M. Sc. [IV Pharmacol.] 14 32, 1941)

504 Silverman, L. B.· The treatment of pruritus from chicken pox with Pyribenzamine, J Pediat. 35.442, 1949.

505 Simon, S W., and Seyler, L. E.· Dramamine in pilots, J. Aviation Med. 20 371, 1949

506. Slater, B J, and Francis, N Benadryl, a contributing cause of an accident, J A. M. A. 132·212, 1946

507. Smith, W, and Humphrey, J H.· The effect of sodium salicylate upon hypersensitivity reactions, Brit. J Exper. Path. 30 560, 1949

508 Snyder, F H, Klahm, G R., and Werner, H. W.: Studies on the metabolism of 2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl]-pyridine succinate (Decapryn succinate), J. Am. Pharm. A. 37 420, 1948

509. Sondern, C. W., and Breivogel, P. J · N,N-dimethyl-N'-benzyl-N'-2-thiazolylethylenediamine, U. S Patent No 2440703, May 4, 1948

510 Southwell, N "Antihistan" in treatment of asthma and hay-fever, Brit. M. J. 1·877, 1948

511 Spain, W. C., and Pflum, F. A.: An evaluation of the present status of antihistaminic substances, New York State J. Med. 48 2272, 1948.

512 Sperber, N; Papa, D, Schwenk, E., and Sherlock, M.: Pyri-

531 Sutherland, J M.: Two cases of periarteritis nodosa, with observations on aetiology, diagnosis and treatment, Brit. M. J 1 832, 1948.
532 Swanberg, H. The source of the histaminolytic enzyme in the blood of pregnant women, Acta physiol. Scandinav. 16 83, 1948
533 Swartz, H Untoward side-effect following Benadryl administration, New York State J. Med. 48 88, 1948.
534 Swyer, G I. M.. Antihistamine effect of sodium salicylate and its bearing upon the skin-diffusing activity of hyaluronidase, Biochem. J. 42 28, 1948
535. Taub, S J.; Miller, R. E., and Taub, R. G A clinical investigation of Tagathen (chlorothen citrate) (N,N-dimethyl-N'-(2-pyridyl)-N'-(5-chloro-2-thenyl) ethylenediamine dicitrate) with a comparison of various antihistaminic agents, Am. Pract. 3 586, 1949.
536. Tebrock, H E. Management of the common cold with Neohetramine (Anahist) A preliminary report, Indust. Med & Surg 19 39, 1950
537 Thomas, W A., and Butler, S Treatment of migraine by intravenous histamine, Am. J Med 1 39, 1946
538. Tislow, R., Labelle, A., Makovsky, A. J, Reed, M. A. G; Cunningham, M. D; Emele, J F. Grandage, A., and Roggenhofer, R. J M. Pharmacological evaluation of Trimeton, 1-phenyl-1-(2-pyridyl)-3-N,N-dimethylpropylamine, and Chlor-Trimeton, 1-(p-chlorophenyl)-1-(2-pyridyl)-3-N, N-dimethylpropylamine, Federation Proc. 8 338, 1949.
539 Tobias, M Anthisan poisoning, Brit. M. J. 1 1098, 1949 (correspondence)
540 Traub, T B, Friedemann, U, and Landstadt, D.: A new method for quantitative evaluation of activity of antihistaminic substances and its application to the study of β-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl), J Allergy 18 273, 1947
541 Troescher-Elam, E., Ancona, G R., and Kerr, W. J. Histamine-like substance present in nasal secretions of common cold and allergic rhinitis, Am. J Physiol. 144.711, 1945
542 Tweedall, D C., and O Connor, W. B. Pyribenzamine in therapy and prophylaxis of rhus dermatitis, J Invest. Dermat. 10 301, 1948

557. Waldriff, G A.; Davis, J., and Lewis, G. M.. Antihistaminic drugs in dermatologic therapy, Arch Dermat & Syph 61 361, 1950

558 Watanabe, K.. Quantitative Untersuchungen über den gehalt an darkmontrahierenden Stoffen von Lunge und Leber bei Meerschweinchen in Stadium der Eiweissensibilisierung und im anaphylaktischen Shock, Ztschr f Immunitätsforsch. u. exper Therap 72·50, 1931

559 Way, E L., and Dailey, R. E. Adsorption, distribution and excretion of tripelennamine (Pyribenzamine), Proc. Soc Exper Biol. & Med 73 423, 1950.

560. Weeks, R E., and Gunnar, R. M. Effect of tripelennamine hydrochloride on acute inflammation, Arch Path. 48 178, 1949

561 Weil, H Unusual side effects from Benadryl, J A. M. A. 133 393, 1947

562 Weiser, R. S., Evans, E., and St. Vincent, L. Tuberculin reaction IV Failure of Pyribenzamine to protect against systemic tuberculin shock, Proc. Soc Exper Biol. & Med. 73 303, 1950

563 Weiser, R. S, Golub, O J, and Hamre, D M Studies on anaphylaxis in the mouse, J Infect Dis. 68 97, 1941

564 Weiss, W I, and Howard, R. M Antihistamine drugs in hay fever A comparative study with other therapeutic methods, J Allergy 19 271, 1948

565 Wells, H G The present status of the problems of anaphylaxis, Physiol. Rev 1 44, 1921

566 Wells, H G *The Chemical Aspects of Immunity* (ed 2, New York The Chemical Catalogue Co, 1925).

567 Wells, J A, Gray, J S, and Dragstedt, C. A. An investigation of the question of histamine tolerance, J Allergy 13 77, 1941

568 Wells, J A., and Morris, H C. Observations on the antagonism of histamine by β-dimethylaminoethyl benzhydryl ether (Benadryl), Federation Proc. 4 140, 1945

569 Wells, J A, Morris, H C, Bull, H B, and Dragstedt, C. A. Observations on the nature of the antagonism of histamine by 3-dimethylaminoethyl *benzhydryl* ether (Benadryl), J Pharmacol & Exper Therap. 85.122, 1945

570 Wells, J A., Morris, H C., and Dragstedt, C. A.· Modifica-

84 Yonkman, F. F., Oppenheimer, E., Rennick, B., and Pellet, E., Pharmacodynamic studies of a new antihistaminic agent, Pyribenzamine (N,N-dimethyl-N'-benzyl-N'-(α-pyridyl)-ethylenediamine hydrochloride). II Effects on smooth muscle of the guinea pig and dog lung, J Pharmacol. & Exper Therap 89 31, 1947
85 Yonkman, F F, Roth, F, Smith, J, Hansen, N., and Craver, B N, Local anesthetic properties of Antistine and Pyribenzamine hydrochloride, Anesth & Analg 28.170, 1949
86 Zeller, M. Nasal Pyribenzamine for relief of hay fever, Ann. Allergy 7 103, 1949

Index

A

Acetomine, 227
Acetophenetidin with antihistamines, 183, 221 ff
Acetylcholine spasmogenic action, 63 f
Acrosclerosis, 150
Administration, 168 ff
  aerosols, 113 f, 188 f
  of combined drugs, 180 ff, 220 ff
  eye drops, 148 f, 186 f
  frequency of, 176 ff
    in nasal allergies, 106 f
  intravenous or intramuscular, 185 f
  by iontophoresis, 165, 189
  nasal application, 107, 187 f
  oral, 107, 183 f
    day and evening, 177
    duration of effect, 176 f
    elixirs, 184
    enteric coating for, 107, 184
  rectal, 186
  selection of antihistamine, 178 ff
  self medication — hazards, 213 ff
  topical, 141 f, 148 f, 189 f.
    toxic reactions to, 207
Adrenocorticotrophic hormone antiallergic effects, 30 f, 218
Aerosols
  for asthma, 113 f, 127, 188 f
  in prevention of anaphylaxis, 77
Agranulocytosis from antihistamines, 206 f
AH289, *see* Chlorcyclizine
Airsickness, 159 f
Albuminuria, orthostatic, 71
Alertness, diminution of, with antihistamines, 193
Allergy, *see also* specific conditions
  to aspirin, 183
  causing cough, 112 ff, 122
  desensitization in, *see* Desensitization therapy
  differentiated from common cold, 106, 157 f
  food, therapy, 192
  gastrointestinal, 158 f
  histamine concept of, 16 ff, 23 f
    objections to, 17 f

pharmacodynamics of, 55 ff
poisoning, course and therapy, 212 f.
potency
assay methods, 50 f, 61 f., 86 ff
experimental vs. clinical, 86 f.
with prolonged action, 118, 125
proprietary preparations, 220 ff.
results of questionnaire on, 215
selection of, 178 ff
self-medication—hazards, 213 ff
sensitization to, 209
therapy
evaluation, 88 ff, 108 f, 217 ff.
failure, 105, 113
limitations, 191 f
Antihistaminogenesis, 32 f
Antistine
antianaphylactic activity, 77
for atopic dermatitis, 140
chemistry, 47
dosage, 115, 172, 173
effectiveness, 47
effect on bronchoconstriction, 60
eye drops, 115, 149, 186 f
sensitization to, 208
histamine flare inhibition, 96, 98
in ocular allergy, 148 f
preparations, 220
in respiratory allergy, 115
toxicity, 196 f
for urticaria, 133
Antopic cream, 228
APC with antihistamines, 183, 220 ff
Arrhythmia from antihistamines, 196
Arthus reaction, 81 f
Aspirin with antihistamines, 183
Asthma
aerosols for, 113 f, 127, 188 f.
antiasthmatic therapy, 31, 112, 182
Benadryl for, 116 f
causing aggravation of, 198
cardiac, 117
desensitization in, 105
in hay fever, 105, 192
histamine, in bioassay, 93
histamine in, 22, 23 f
-excess hypothesis, 113
respiratory function studies, 113
response to antihistamines, 105, 112 ff

B

Bacteria sensitivity reactions—effect of antihistamines on, 72, 82
Barbiturates action with antihistamines, 58
Barium spasmogenic action, 63 f
Bee stings, 166
Benadryl
aerosols, 188 f.
antianaphylactic activity, 77, 80 f.
anticholinergic action, 116
as antiemetic, 160 f.
antispasmodic action, 58
for asthma, 116 f
causing aggravation, 198
for atopic dermatitis, 140
chemistry, 44 f
in collagen diseases, 149 f
for contact dermatitis, 143
cutaneous reaction to, 209
for dermographism, 139, 185
dosage, 172, 173

preparations, 221
prolonged action of, 118
for respiratory allergy, 117 f.
toxicity, 118, 198
for urticaria, 134
Chlorothen
antianaphylactic activity, 78
for atopic dermatitis, 141
chemistry, 40
dosage, 119, 172, 173
effectiveness, 40
effect on bronchoconstriction, 60
histamine flare inhibition, 96
preparations, 221
for respiratory allergy, 119
toxicity, 198
for urticaria, 135
8-Chlorotheophylline: for air-sickness, 160
Chlorprophenpyridamine maleate, 222
Chlor-Trimeton
antianaphylactic activity, 78
for atopic dermatitis, 140
chemistry, 46
for contact dermatitis, 143
dosage, 120, 172, 173
effectiveness, 46 f
effect on bronchoconstriction, 60
preparations, 222
for respiratory allergy, 120 f
toxicity, 121, 198 f.
for urticaria, 134
Circulatory system: toxic effects of antihistamines, 205 f
Cohistine, 226
Cold
sensitivity to, 167
Cold, common
antihistamines in, 151 ff
basis for trial of, 151 ff
claims for success of, 153 ff
as failure of, 155 ff.
differentiated from allergy, 106, 157 f
histamine in secretions of, 152
incidence during antihistamine therapy, 158
self-diagnosis, 213
self medication, 213 ff.
Collagen diseases, 149 f
Conjunctivitis
allergic, 115, 148, 187
nonbacterial, 148
phlyctenular, 148, 149
response to antihistamines, 148 f.
Convulsions: from antihistamines, 164, 194
Corenil, 225
Coricidin, 222
Cortisone: antiallergic effects, 30 f, 218
Cough
allergic, 112 f., 122
preasthmatic, 112
Cream, Pyribenzamine, 143, 189, 229
Crotalin: in anaphylaxis, 29
Curare effects: antihistamines in, 166

D

Dasikon, 225
Deaths due to antihistamines, 209 ff.
Decapryn
in allergic dermatitis, 83
antianaphylactic activity, 78, 80
chemistry, 45
dosage, 121, 172, 174
effectiveness, 45
effect on bronchoconstriction, 60
effect on histamine flare, 96
in peptic ulcer and acute gastritis, 159
preparations, 222
for respiratory allergy, 121
toxicity, 199

Doses table of, 172
Doxylamine succinate, 222
Dramamine
for motion sickness, 159 f.
for nausea of pregnancy, 160
preparations, 221
for radiation sickness, 162
side actions, 160
toxicity, 199
Dysmenorrhea, 164 f.

E

Eczema, *see also* Dermatitis, atopic
palpebral, 148
Edema
angioneurotic, 132 f.
from egg white, in rat, 84 f.
laryngeal, 133, 185
pulmonary, from epinephrine, 70
in urticaria, 132
883F effect on tuberculin reaction, 82
Electrocardiogram changes in, from antihistamines, 205 f.
Electroencephalogram abnormalities, and antihistamines, 164
Endophthalmitis phacoanaphylactica, 148
Environment variables in, in hay fever, 90
Ephedrine
in asthma, 34, 182
combined with antihistamines, 181 f.
Epilepsy antihistamines in, 164
Epinephrine
in allergic emergencies, 133 185
in asthma and allergy, 33 f., 113
causing pulmonary edema, 70
causing ventricular fibrillation, 72
effect on histamine action, 25
for serum sickness, 138
Episcleritis, 149
Erythema multiforme, 144
Ethanolamine derivatives, 44 ff.
Ethers, phenolic combating histamine, 31 f.
Ethylenediamine derivatives, 36 ff.
Excitation, 194 f., 196
in children, 107
with Thephorin, 128, 202
Eye drops
Antistine, 115, 149, 156 f.
concentration, 157
Histadyl, 149, 157
Eyes
action of histamine on pupil, 55
allergic conditions, 147 ff.
local anesthesia with antihistamines, 57
recurrent erosion, 149
topical use of antihistamines in, 149, 156 f.
toxic reactions to antihistamines, 205, 209

F

Federal Trade Commission, 216
Fernozydyne, 221
Fibrillation, ventricular, experimental, 72
5512M (Ciba) in experimental nephritis, 85
Flavonoids antianaphylactic effects, 32 f.
Fluorescein change in capillary permeability, 67
p-Fluorobenzyl DPE (Lederle)
antianaphylactic activity, 79
for atopic dermatitis, 142
chemistry, 43
dosage, 130, 172, 175 f.
effectiveness, 43
effect on bronchoconstriction, 60

cutaneous reaction to, 53, 65, 67, 93 ff.
desensitization, 17, 25 ff
-excess hypothesis, 105, 113
-inhibiting agents, 29
metabolism, 21 f.
minimum lethal dose, 61
multiple lethal doses, 62
pharmacologic effects, 20, 52 ff.
physiologic actions, 20 ff.
release mechanism, 15 f., 23 f.
in secretions of common cold, 152
in tissues, 14, 17, 23 f.
tolerance for, 26
wheal and flare
inhibition, in assay of antihistamines, 93 ff
species difference, 67
Histidine decarboxylase in histamine formation, 32
Hyaluronidase and spread of allergic reactions, 71
Hydryllin, 122 f
dosage, 122, 172, 174
effectiveness of, 182
histamine flare inhibition, 98
in nasal allergy, 108
preparations, 220 f
toxicity, 197, 200
Hyoscine for motion sickness, 160
Hyperglycemia from Benadryl, 71
Hypersensitivity
Arthus reaction, 81 f
experimental, 73 ff
cardiovascular, 83 f
to injected agents, 146
responses other than histamine in, 87
to tuberculin, 82 f
Hypertension, 56
from antihistamines, 196, 206
in pregnancy, 166
Hypotension, from antihistamines, 56, 196

I

Ileum, guinea pig: in experimental evaluation of antihistamines, 62 f., 81
Infections
chronic nasal, antihistamines in diagnosis, 106
spread of, with antihistamines, 66 f., 165 f
Insect bites, 144, 166
Insulin allergy to, 147
Intestines
antihistamine effects — experimental, 62 ff., 81
untoward effects of antihistamines, 195
Iodides for asthma, 34, 182
Iontophoresis, 165
nasal, 189
for pruriginous dermatitis, 189
Iridocyclitis, 148
Iritis, 149
Isuprel for asthma, 112, 182

J

Jaundice
from antihistamine, 210
pruritus of, antihistamines for, 144

K

Keratoconjunctivitis, 148

L

Labyrinthitis, acute from Benadryl, 205
Lacrimation histamine in, 70
Leg cramps nocturnal, 163
Lichen chronicus circumscriptus, 144
Lichen simplex chronicus, 144, 189

histamines, 164, 203 ff.
side actions of antihistamines, 194
Nethaphn, 222
Neuralgia, trigeminal, 163
Neuritis from Benadryl, 204
Neurodermatitis, disseminated, 142
929F
antianaphylactic activity, 44, 76
chemistry, 44
effect on bronchoconstriction, 60
Norisodrine for asthma, 112, 182
Nose drops, 187
Nuclon, 226

O

Ointment
Pyribenzamine, 141, 165, 189, 208
Thephorin, 142, 144, 190, 209
1571F
antianaphylactic activity, 76, 80 f
chemistry, 36 f
effectiveness, 37
effect on bronchoconstriction, 60
1627 (Searle), in experimental cardiovascular lesions, 84
1694 (Searle) in experimental cardiovascular lesions, 84
194B (White)
antianaphylactic activity, 78
chemistry, 42
dosage, 172, 176
effectiveness, 42 f
effect on bronchoconstriction, 60
histamine flare inhibition, 96
for respiratory allergy, 130
toxicity, 130, 202 f
Ophthalmia, sympathetic prevention, 148
Orthoxine
antianaphylactic activity, 79
for asthma, 182

P

Paraminyl maleate, 226
Parkinson's disease, 162 f
Penicillin reactions, 136
hazard of antihistamine prophylaxis, 138
Pentryl, 223
Peptic ulcer, 159
Perazil, *see also* Chlorcyclizine
preparation, 221
Periarteritis nodosa, 149
experimental, inhibition, 83 f
Phenergan
antianaphylactic activity, 77
for atopic dermatitis, 141
chemistry, 38 f.
dosage, 125, 172, 175
effectiveness, 39
effect on allergic wheal by, 99 f
effect on bronchoconstriction, 60
histamine flare inhibition, 96, 98
for migraine, 163
for nausea and vomiting of pregnancy, 160
prolonged action of, 125
for respiratory allergy, 125 f
side actions, 125
for urticaria, 135
Phenindamine tartrate, *see also* Thephorin
preparations, 230 f
Poison ivy, 143
Potassium in experimental allergy, 29 f
PPA capsule, 228

from Neo-Antergan, after irradiation, 161
Reiter's syndrome, 148
Renstamine, 228
Respiration effect of antihistamines on, 56
Respiratory system
in anaphylaxis, 74
function studies, in asthma, 113
Rheumatic fever, 150, 206
Rhinitis
chronic vasomotor, 105
perennial vasomotor, 103 ff
clinical results with individual drugs, 114 ff
dosage and administration of antihistamines, 106 ff
incidence of antihistamine effect, 108 ff

S

Salicylates
antihistaminic effects, 30
for serum sickness, 137
Scleritis, 148
Scleroderma, 150
Sclerosis, multiple, 163
Seasickness, 159 f
Secretions
gastric
effect of antihistamines, 68 f., 158 f.
histamine action on, 54
glandular
effect of antihistamines, 68 ff
histamine action on, 21
nasal, drying of, 195
Sedscof 226
Sedation, 58, 193 f
antihistamines for, 167
in asthma therapy, 34, 113
in atopic dermatitis, 140
in choice of drug, 179
and frequency of administration, 177
and size of dose, 171
Sedatives with antihistamines, 181
Semikon, 225
Serum sickness, 136 f.
hazard of prophylactic therapy, 138
Shock
anaphylactic, see Anaphylaxis
in burns, histamine in, 67 f
hemorrhagic, histamine in, 68
histamine, 13 ff
prevention, 62, 79, 87
species difference, 73
Side actions, see also Toxic effects
advantageous, 167, 192
common and minor, 192 ff
Skin
eruptions, from antihistamines, 207 ff
tests
in assay of antihistamines, 93 ff, 99 f
prevention of dermographism in, 138 f
topical use of antihistamines on, 189 f
Status asthmaticus
Benadryl intravenously for, 186
hazard of antihistamine therapy, 210
Stimulants
for antihistamine poisoning, 212
combined with antihistamines, 181
Streptomycin therapy reactions, 160
Sulfonamide reactions hazard of antihistamine prophylaxis, 138
Sunburn prevention, 165
Suppositories, antihistamine, 186

Tripelennamine hydrochloride, *see also* Pyribenzamine preparations, 229
Tuberculin sensitivity effect of antihistamines on, 82 f., 150 f
Tuberculosis, 150 f
2339RP, *see* Antergan
2325RP antianaphylactic activity, 76, 80 f.

U

Ulcers, gastric from histamine, 69
Ultraviolet rays absorption of, by antihistamines, 165
Urinary disturbances from antihistamines, 196, 201
Urticaria
from antihistamines, 208
response to antihistamines, 131 f
Uterus
action of histamine on, 51 f
effects of antihistamines on, 64
Uveitis, anaphylactic prevention, 85, 148

V

Vascular system
effect of antihistamines on, 66
histamine action on, 22 f.
Vomiting
from antihistamines, 195
postoperative, 161
of pregnancy, 160

W

Wheal and flare reaction
to codeine, 67
to histamine, 21, 93 f
inhibition of, 91 ff, 97 ff.

Z

01003 (Lilly)
antianaphylactic activity, 78
effect on histamine flare, 96
01780 (Lilly)
antianaphylactic activity, 78
effect on histamine flare, 96